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IMPROVEMENT OPPORTUNITIES IN THE MULTIMODAL TREATMENT OF PEDIATRIC BRAIN TUMORS

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Für Sarah, weil mit ihr kein Drache jemals zu groß war

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ABBREVIATIONS

aHSCT	Autologous Hematopoietic Stem Cell Transplantation
ATRT	Atypical Teratoid Rhabdoid Tumor
CI	Confidence Interval
CNS	Central Nervous System
COG	Children's Oncology Group
CSI	Craniospinal Irradiation
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
ET	Embryonal Tumors
ETANTR	Embryonal Tumor with Abundant Neuropil and True Rosettes
ETMR	Embryonal Tumor with Multilayered Rosettes
GTR	Gross Total Resection
HART	Hyperfractionated Accelerated RadioTherapy
HNJ	Hospital Niño Jesús, Madrid
HR	High Risk
IMRT	Intensity Modulated Radiation Therapy
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NTCP	Normal Tissue Complication Probability
OS	Overall Survival
PB	Pineoblastoma
PFS	Progression Free Survival
PNET	Primitive NeuroEctodermal Tumors
PT	Particle Therapy
QA	Quality Assurance

QI	Quality Indicator
QOL	Quality Of Life
QUARTET	QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials
RCT	Randomized Clinical Trial
RT	Radiotherapy
RTQA	Radiotherapy Quality Assurance
SEHOP	Spanish Society of Pediatric Hematology and Oncology
SHH	Sonic Hedgehog
SIOPe	European Society of Pediatric Oncology
SR	Standard Risk
STR	Subtotal Resection
WHO	World Health Organization
WNT	Wingless

SUMMARY

The treatment of pediatric CNS tumors remains one of the major challenges in modern pediatric oncology. The general aim of this study is to improve the management of these patients, on a multilevel approach: At an institutional/local, national and international/European level. Three research projects were carried out:

In Research Project #1, a monocentric review of all pediatric patients with medulloblastoma treated between 2003 and 2016 at Hospital Niño Jesús, Madrid, was performed. While the global outcome of the 58 included patients was similar to the outcome observed in European population-based studies (5-year OS: 59%), several measures were proposed to improve the identified weak areas. These measures include implementing a quality assurance system, promoting the inclusion in international clinical trials, establishing a central pathology review, accelerating the translation of the new molecular knowledge into daily practice, and implementing a neurocognitive and QOL evaluation program. Moreover, a set of 27 quality indicators to evaluate the management of these patients was developed.

In Research Project #2, all pediatric patients with non-medulloblastoma CNS embryonal tumors treated in eight major oncology centers in Spain between 2005 and 2014 were reviewed. The 43 included patients presented a dismal outcome (3-year OS: 35%), especially when compared to patients included in clinical trials. Establishing a common national strategy, implementing referral circuits and collaboration networks, and incorporating new molecular knowledge into routine clinical practice were proposed as accessible measures that can improve the outcome of these patients. Additionally, a retrospective molecular analysis (methylation profiling) of tumor samples of this patient cohort was started.

In Research Project #3, the radiotherapy quality assurance (RTQA) systems in past and current clinical trials protocols for pediatric CNS tumors were analyzed. Several initiatives to implement RTQA, both at national and international levels, are being developed across Europe. Furthermore, a survey about the practices of RTQA in pediatric CNS tumors across 21 European countries was performed. As a result, five key measures were proposed: Creating a European RTQA guideline for pediatric CNS tumors, improving the collaboration between pediatric oncologists and radiation oncologists, building a European central storage system for RT data, implementing international RTQA platforms, and promoting European referral networks to reduce inequality.

Overall, this thesis shows that there are several aspects to be improved in the management of pediatric patients with CNS tumors, and proposes a set of pragmatic measures with a three-level approach: local, national and international. Hopefully, this work will contribute to the global improvement of survival and quality of life of children and adolescents with CNS tumors.

RESUMEN EN ESPAÑOL

El tratamiento de los tumores pediátricos del sistema nervioso central (SNC) continúa siendo uno de los mayores retos de la oncología pediátrica contemporánea. El objetivo global de este estudio es mejorar el manejo de estos pacientes a varios niveles: institucional/local, nacional e internacional/europeo. Para ello se han desarrollado tres proyectos:

En el Proyecto de Investigación #1 se realizó una revisión monocéntrica de todos los pacientes pediátricos con meduloblastoma tratados entre 2003 y 2016 en el Hospital Niño Jesús, Madrid. Aunque la supervivencia global de los 58 pacientes incluidos fue similar a la observada en estudios poblacionales europeos (SG a 5 años: 59%), se propusieron varias medidas para mejorar los puntos débiles. Estas medidas incluyen implementar un sistema de calidad, promover la inclusión en ensayos clínicos internacionales, establecer una revisión central de la anatomía patológica, acelerar la translación del nuevo conocimiento molecular a la práctica clínica, e implementar un programa de evaluación neurocognitivo y de la calidad de vida. Además, se desarrolló un conjunto de 27 indicadores de calidad para evaluar el manejo de estos pacientes.

En el Proyecto de Investigación #2, se revisaron todos los pacientes pediátricos con tumores embrionarios del SNC no-meduloblastoma tratados en ocho grandes centros oncológicos en España entre 2005 y 2014. Los 43 pacientes incluidos presentaron un pronóstico desfavorable (SG a 3 años: 35%), especialmente al compararlos con pacientes incluidos en ensayos clínicos. Se propusieron las siguientes medidas asequibles para mejorar el desenlace de estos pacientes: establecer una estrategia nacional común, implementar circuitos de derivación y redes de colaboración, e incorporar los nuevos conocimientos biológicos a la práctica clínica. Además, se inició un análisis retrospectivo molecular (perfil de metilación) de las muestras tumorales de esta cohorte de pacientes.

En el Proyecto de Investigación #3, se analizaron los sistemas de control de calidad de la radioterapia a través de los protocolos de ensayos clínicos actuales y pasados sobre tumores pediátricos del SNC. Se observó que se están desarrollando en Europa diversas iniciativas para implementar un sistema de control de calidad de la radioterapia tanto a nivel nacional como internacional. Además, se llevó a cabo una encuesta sobre las prácticas de control de calidad de la radioterapia en tumores pediátricos del SNC en 21 países europeos. Como resultado de esta encuesta, se propusieron cinco medidas clave: crear una guía europea para tumores pediátricos del SNC, mejorar la colaboración entre oncólogos pediátricos y radio-oncólogos, construir un sistema central europeo de almacenaje de datos sobre radioterapia, implementar plataformas internacionales de control de calidad de la radioterapia, y promover redes de colaboración y derivación europeas para disminuir la desigualdad entre países.

Globalmente, esta tesis evidencia que hay varios aspectos a mejorar en el manejo de los pacientes pediátricos con tumores del SNC, y en ella se propone un conjunto de medidas pragmáticas a tres niveles: local, nacional e internacional. Esperamos que este trabajo contribuya a la mejoría global en la supervivencia y calidad de vida de los niños y adolescentes con tumores del SNC.

I. INTRODUCTION

1. Primary malignant CNS tumors in childhood

Primary malignant central nervous system (CNS) tumors are the second most common childhood malignancies, after hematologic malignancies [1–3]. Their estimated incidence varies among different US and European studies (2.6-5.4 cases per 100,000 person-years for children and adolescents) [4–6].

Primary CNS tumors are a heterogeneous group of neoplasia derived from different brain or spinal cord progenitor cells. Their classification has been based largely on histological features for the past century, with a complex and steadily changing scheme [7]. This relies above all on their diverse and insufficiently known underlying biology. However, efforts are being made to improve the characterization of each tumor entity. In fact, the latest version of the World Health Organization (WHO) classification includes not only histology, but also genetic and molecular features as key tools for an accurate diagnosis [8]. According to this classification, the two most common CNS tumor groups in children are astrocytic and embryonal tumors.

Although advances in surgical intervention, radiotherapy and chemotherapy have improved the survival rates in children with CNS tumors over the last 40 years, unacceptable mortality and morbidity rates associated with these disorders persist. They constitute the leading cause of death from cancer in children, with a 10-year overall survival (OS) for children <15 years of 65.7-76.1% [9]. Furthermore, survivors face significant sequelae, mainly deriving from the complications of surgery and craniospinal radiotherapy.

Hence, the treatment of pediatric brain tumors remains one of the major challenges in modern Pediatric Oncology. The general aim of this study is to improve the management of these patients, on a multilevel approach: At an institutional/local, national and international/European level.

2. CNS embryonal tumors

Embryonal tumors (ET) account for 25% of all CNS tumors in patients under 18 years. This percentage rises up to 40% when only malignant CNS tumors are included. Their treatment is associated with some mortality and high morbidity with significant sequelae secondary to surgery, chemotherapy and, above all, radiotherapy.

CNS-ET affect most frequently young children, with over 20% of them in patients <3 years, which hinders their diagnosis and management.

As detailed in the WHO classification, CNS-ET have a heterogeneous biology. They are highly aggressive tumors (grade IV histology), with a marked tendency to spread among the CNS axis.

This tumor group includes medulloblastoma, CNS primitive neuroectodermal tumors (PNET), and atypical teratoid rhabdoid tumors (ATRT), among other rare subtypes. Although these tumors have been formerly classified as "primitive neuroectodermal tumors", this larger group has been repeatedly splitting up over the last decades into smaller, more accurately defined groups. The growing cytogenetic and molecular knowledge has led to differentiate them as distinct histologic entities.

In this steadily changing scenario, the term "PNET" has suffered the most. When medulloblastoma was separated to an own category, the term "supratentorial PNET" was used to define all embryonal tumors that were not medulloblastoma. This mixed group was once again redefined in the 2007 WHO classification to "CNS-PNET", distinguishing between different subtypes as "CNS neuroblastoma", "CNS ganglioneuroblastoma", "Medulloepithelioma", and "Ependymoblastoma" (Table 1). In the latest 2016 upgrade, the term "PNET" is abandoned, and new, specific entities emerge, such as "embryonal

tumor with multilayered rosettes", ETMR (former "embryonal tumor with abundant neuropil and true rosettes", ETANTR) (Table 2).

Pineoblastoma, although recently reclassified by the WHO to the group of "Tumors of the pineal region", has been historically included in the group of "Embryonal tumors" due to its aggressive histologic and clinical features.

Embryonal tumors (2007)
Medulloblastoma Desmoplastic/nodular medulloblastoma Medulloblastoma with extensive nodularity Anaplastic medulloblastoma Large cell medulloblastoma
CNS primitive neuroectodermal tumor CNS Neuroblastoma CNS Ganglioneuroblastoma Medulloepithelioma Ependymoblastoma
Atypical teratoid / rhabdoid tumor

TABLE 1 The 2007 WHO classification of embryonal tumors. Adapted from [7].

Embryonal tumors (2016)
Medulloblastomas, genetically defined Medulloblastoma, WNT-activated Medulloblastoma, SHH-activated and TP53-mutant Medulloblastoma, SHH-activated and TP53-wildtype Medulloblastoma, non-WNT/non-SHH Medulloblastoma, group 3 Medulloblastoma, group 4
Medulloblastomas, histologically defined Medulloblastoma, classic Medulloblastoma, desmoplastic/nodular Medulloblastoma with extensive nodularity Medulloblastoma, large cell / anaplastic
Medulloblastoma, NOS
Embryonal tumor with multilayered rosettes, C19MC-altered
Embryonal tumor with multilayered rosettes, NOS
Medulloepithelioma
CNS neuroblastoma
CNS ganglioneuroblastoma
CNS embryonal tumor, NOS
Atypical teratoid/rhabdoid tumor
CNS embryonal tumor with rhabdoid features

TABLE 2 The 2016 WHO classification of embryonal tumors. Adapted from [8].

2.1. Medulloblastoma

Medulloblastoma is the most common malignant CNS tumor of childhood, accounting for 20% of all primary CNS tumors among children. Its primary site occurs exclusively in the cerebellum (posterior fossa). However, today is clear that medulloblastoma constitutes a unique entity with distinct clinical and biological features, far beyond its location.

Patients with medulloblastoma present symptoms derived from increased intracranial pressure and cerebellar dysfunction. They are often unspecific and evolve over weeks or months, which can lead to delayed diagnosis, particularly in young children.

Magnetic resonance imaging (MRI) typically shows a contrast-enhancing midline or paramedian cerebellar mass [10], but diagnosis requires histopathologic confirmation. Approximately one third of patients have disseminated disease at diagnosis. Staging should include spinal MRI and cerebrospinal fluid cytology obtained preoperatively or two weeks after surgery (to avoid contamination with surgical debris) [11–13].

Age, extent of disease, extent of resection, histopathologic subtype and, recently, molecular subtype are used to stratify patients with medulloblastoma into risk groups.

Children younger than 3-5 years have a significantly poorer prognosis, with negative impact on both survival and quality of life. This is partly explained by the need to avoid craniospinal radiotherapy in very young children due to its toxicity to the developing CNS.

The modified Chang criteria are used to evaluate the extent of disease [14, 15], which also has a negative impact on prognosis (progressively worse in the presence of more advanced disease) [16–18]. (Table 3)

Type of metastasis	
M0	No evidence of gross subarachnoid or haematogenous metastasis
M1	Microscopic tumor cells found in the cerebrospinal fluid
M2	Gross nodular seeding demonstrated in the cerebellar/cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in the spinal subarachnoid space
M4	Metastasis outside the cerebrospinal axis

TABLE 3 Modified Chang criteria for the staging of medulloblastoma. Adapted from [14].

Extent of resection is also a major prognostic factor, with gross total or near-total resection (residual tumor <1.5 cm^2) having a demonstrated positive impact on outcome [19].

There are several histopathologic subtypes according to WHO classification (Tables 1 and 2). They constitute important prognostic factors, particularly in young children. Patients with desmoplastic/nodular or desmoplastic with extensive nodularity have significantly better prognosis compared with the classic form of medulloblastoma. In contrast, those with anaplastic/large cell variants show poorer outcome [18].

The knowledge gained on biological features of medulloblastoma over the last few years has led to the characterization of four molecular subgroups, which have distinct histology, genetics, clinical behavior and patient outcomes: sonic hedgehog (SHH), Wingless (WNT), group 3 and group 4 [20–22]. Tumors with activation of the WNT pathway have the best prognosis, in opposition to tumors classified as group 3, which have the worst prognosis [23]. Tumors with

activation of the SHH pathway and those in group 4 have an intermediate prognosis. SHH tumors with TP53 mutations constitute an important exception, with a particularly poor outcome [24]. It is important to note that this biological knowledge keeps evolving rapidly; e.g., some recent studies propose to expand the molecular classification to seven subgroups [25], while others underscore the idea that the currently defined subgroups are likely to be an oversimplification of true molecular substructure [26].

Taking into account the above exposed prognostic criteria (age, extent of disease, extent of resection, histopathologic and molecular subtypes), two major risk groups emerge, consistent among different international workgroups: low/standard (or "average") and high risk.

The combination of surgery, craniospinal irradiation (CSI) and chemotherapy is the standard of care for children with medulloblastoma. Following maximum safe resection, the treatment strategy varies according to age and extent of disease.

The standard risk group includes children older than 3-5 years who have undergone a gross total or near-total resection (tumor residue <1.5 cm^2) and have no evidence of metastases (M0 following modified Chang criteria). After surgery, these children receive CSI and adjuvant chemotherapy. For instance, one of the most accepted treatment schemes was used in the Children's Oncology Group (COG) medulloblastoma trial A9961 [27]. After tumor resection, patients are treated with 23.4 Gy to the craniospinal axis with a posterior fossa boost to a total dose of 55.8 Gy, with weekly concurrent vincristine. This is followed by eight cycles of chemotherapy (cisplatin, vincristine, cyclophosphamide, CCNU). The 10-year event-free and overall survival (EFS and OS) rates in this study are 76% and 81% respectively.

The high-risk group includes children with metastatic disease, residual tumor (≥1.5cm^2), or those with adverse histological or biological features (large cell/anaplastic subtype, extensive nodularity, MYC or MYCN amplification). Their optimal treatment is still unknown, but most trials include CSI given at higher doses with concurrent chemotherapy followed by combination chemotherapy. There are multiple approaches, for example HART-Milan [28] and the more recent COG-ACNS0332 (NCT00392327). In the HART-Milan strategy, patients received postoperative chemotherapy in a two-month schedule (methotrexate, etoposide, cyclophosphamide, carboplatin), then hyperfractionated accelerated radiotherapy (HART) with 39 Gy to the neuraxis and a posterior fossa boost of 60 Gy. Patients with persistent disseminated disease before HART were consolidated with two myeloablative courses and autologous hematopoietic stem cell transplant (aHSCT) (tandem aHSCT). The 5-year EFS and OS in the original trial were 70% and 73% respectively [28]; however, these positive results have not been reproduced in real-life settings, and concerns about toxicity have reduced its use [29]. In the COG-ACNS0332 trial (NCT00392327), patients receive standard therapy consisting of surgery, radiotherapy (36 Gy to the neuraxis and 55.8 Gy to the posterior fossa) and maintenance chemotherapy (cisplatin, vincristine, cyclophosphamide). Subsets of patients are randomly assigned to receive carboplatin radiosensitization, isotretinoin during maintenance, both, or neither.

Infants and young children (< 3-5 years) with medulloblastoma are at risk of severe neurologic impairment if their initial treatment includes CSI. A cut-off age of 3 years is widely accepted; it was introduced in the 1980s to reduce unacceptable sequelae such as severe cognitive decline and impaired spinal growth [30–33]. Hence, the protocols designed for these patients use combination chemotherapy to either delay or avoid radiotherapy. They often include high-dose chemotherapy. For instance, the Head Start I and II

strategies in non-metastatic medulloblastoma obtained a 5-year EFS and OS of 52% and 70% [34]. However, the long-term effectiveness of substituting chemotherapy for CSI remains uncertain. In addition, the increased risk of second malignancies is a concern [35].

In the recently implemented clinical trials such as SIOP-PNET5 (NCT02066220), histopathologic and molecular features of the tumor are being included in the treatment decision algorithms. For instance, extended nodularity in young children is considered a good prognostic factor creating a new category of "low-risk" patients, which will receive treatment reduction.

Despite undergoing optimal first line treatment, 20-30% of children with medulloblastoma will experience relapse, either locally or among the neuraxis [36, 37]. The likelihood of long-term survival after relapse is close to zero. Salvage radiotherapy in young children or aHSCT in older children are widely used approaches that may achieve a prolonged disease-free survival [38–42].

New therapies are emerging, aiming inhibition of molecular targets involved in the pathogenesis of medulloblastoma, especially for the SHH pathway tumors [43]. In this regard, vismodegib is a promising targeted therapy for SHH-driven cases [44–46].

For infants younger than three years, only 40-50% of patients survive, partly due to the reduction or withdrawal of radiotherapy. Young children with disseminated disease at diagnosis have a particularly poor prognosis, with a 5-year OS of 15-30% [47, 48]. Other prognostic factors have already been explained (residual disease after surgery, histological and molecular features).

Each modality of treatment can cause delayed complications that have a profound effect on quality of life in survivors. The most common long-term sequelae include posterior fossa syndrome, neurocognitive impairment,

hearing loss, endocrine abnormalities, cerebrovascular disease, and second malignancies [35, 49–58]. Therefore, upcoming trials are aimed not only to improve survival, but also to increase the quality of life of survivors, as well as reducing long-term toxicities caused by chemotherapy and radiotherapy.

In Research Project #1, we aim to analyze the management of children with medulloblastoma in a major Spanish oncology institution, in order to identify weak points that ought to be improved in day-to-day practice.

2.2. Non-medulloblastoma CNS embryonal tumors (former PNET)

Non-medulloblastoma CNS embryonal tumors (formerly CNS-PNET) are poorly differentiated, highly aggressive, neuroepithelial tumors that originate from the germinal matrix of the primitive neural tube. They can differentiate to diverse cell lineages, so that, for example, tumors with pure neuronal differentiation are classified as CNS-neuroblastomas, whereas those with mixed neuronal and ganglion cell differentiation are classified as CNS-ganglioneuroblastomas. Some PNET can be classified according to specialized tissue of origin, e.g. pineoblastoma, but most of the remainder originate in the cerebral hemispheres and were therefore previously referred to as supratentorial PNET [7, 8].

Despite the multiple changes that this group of tumors has already experienced in their classification and nomenclature (see section “2. CNS embryonal tumors”), it is foreseeable that the complexity will grow in the near future. Recent epigenetic studies have started a new molecular era in which new entities emerge [59–62]. These new entities include “CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2)”, “CNS Ewing sarcoma family tumor

with CIC alteration (CNS EFT-CIC)", "CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1)", and "CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)".

CNS-PNET account for less than 5% of CNS embryonal tumors, most of them occurring in children younger than 10 years [3, 4]. Symptoms at diagnosis are often unspecific. Older children present signs of increased intracranial pressure (e.g., headache, vomiting), whereas infants show lethargy, irritability, anorexia and enlarged head circumference. Other symptoms may include focal deficits or seizures depending on the tumor location. Leptomeningeal dissemination can be manifested by cranial nerve palsies, spinal cord symptoms or encephalopathy [63]. MRI usually reveals a well-defined, hemispheric mass with heterogeneous enhancement. Calcification, necrotic areas and intratumoral hemorrhage may be present [64].

Traditionally, CNS-PNET have been treated as high risk medulloblastomas. The frontline strategy of non-medulloblastoma CNS embryonal tumors includes aggressive surgical resection followed by CSI [65, 66]. In the German 88/89 and 91 HIT trials, a total CSI of 35.2 Gy and a boost of 20 Gy to the primary tumor site was reported, achieving a 3-year PFS of 49% in children who completed the planned treatment course, in opposition to 7% in those with major radiotherapy deviations. Delayed start of radiotherapy (as per use of pre-irradiation chemotherapy) resulted in poorer outcome [67].

Adjuvant chemotherapy may further improve survival, but the optimal chemotherapy strategy is still unknown. Additionally, most regimens have not been specifically designed for PNET, but are similar or the same as those designed for medulloblastoma. They have been historically evaluated in trials with mixed patient populations, e.g. in the HIT 2000 trial [68, 69].

Infants and young children (<3-5 years) are at high risk for severe neurologic sequelae if their initial treatment includes CSI, which makes their management particularly challenging. Prolonged induction chemotherapy regimens have obtained disappointing results, with 5-year OS rates of 15-30% [48, 70–72]. High-dose chemotherapy strategies have shown more promising results, with one study reporting 5-year OS of 49% [73].

Rapid recurrence is common, despite aggressive combined treatment [36].

The reported 3-year OS varies from 48-73% with strategies that include radiotherapy. Infants and young children (<3 years) and patients with pineoblastoma display a worse prognosis [4, 74–77].

In the face of the recently gained knowledge on the biological features of CNS-PNET, efforts should be made to correlate these molecular classifications to clinical outcomes to implement novel and effective therapies [62, 78, 79].

In Research Project #2, we aim to evaluate the current management of children and adolescents with CNS-PNET/pineoblastoma in Spain and put it in the context of international clinical practice, in order to identify areas of improvement at a national level. In addition, we aim to participate in a wider international collaboration study that will perform a biological profile (methylation array), to analyze the available tumor samples of this patient cohort in light of the new epigenetic knowledge.

3. Clinical trials versus real-world data

Despite the general effort to elaborate and implement international protocols for the management of pediatric CNS embryonal tumors, the obtained results are, albeit universally unsatisfying, not homogenous. The most important accomplishments that have been achieved over the past decades are a direct consequence of some outstanding clinical trials among the diversity of studies that have been performed (e.g. [28, 70, 77, 80, 81]).

However, when pioneer protocols obtained from clinical trials in particular institutions are brought to general clinical practice, the results are recurrently disappointing and never as good as they were originally (e.g. [9, 29, 82]).

Mounting evidence suggests, on the one hand that results pulled outside the context of the clinical trials in which they were acquired are far more unprofitable, and on the other hand that facility standards are crucial to ensure results' optimization. Several differential aspects should be considered when comparing the clinical trial versus the real-world setting, namely the strict patient selection of trials versus the unselected real-world population; the more exhaustive and systematized monitoring and follow-up of patients throughout treatment and after end-of-treatment in clinical trials; the wide implementation of centralized reviews in clinical trials (e.g. central pathology, molecular, or imaging review); and the multi-centric organization of most trials.

In this thesis, we present two real-world data cohorts, one monocentric for medulloblastoma (Research Project #1), and one multi-centric and national for CNS-PNET (Research Project #2), to identify weak points and propose action points to close the gap between real-life and clinical trial patients.

To better understand both projects, it is important to underscore that, while academic clinical trials are the standard of care in pediatric oncology, those trials are not uniformly available. In Spain, no international phase 3 medulloblastoma trials were open over the last decade until very recently; however, SIOP-PNET 5 (NCT02066220) is open in 20 Spanish institutions (the first one opening in 2016). For PNET, no trials have ever been available in this country. This means that almost all patients included in Research Project #1 and all patients of Research Project #2 were treated as "per protocol", as the respective trials were not available at that time, and hence both projects constitute examples of real-world cohorts.

In Research Project #3, the topic of clinical trials versus real-world settings is also discussed. We present an overview of the current situation of radiotherapy quality assurance (RTQA) of pediatric patients with brain tumors in Europe, and our perspective on the challenges and on how to move towards the future, highlighting the importance of addressing the needs of patients treated outside of clinical trials.

4. Clinical audit and quality assurance

The first step towards improvement in the management of complex diseases such as pediatric embryonal brain tumors is to identify the existing weak points. To do so, reviewing past and current clinical practices at different levels (institutional, national and international) is key. Clinical audits and quality assurance programs constitute an essential part of good clinical practice [83, 84]. There is an increasing international interest in the assessment of the quality of childhood cancer care using quality indicators (QIs) [85]. In fact, some important steps have already been taken regarding the definition of the minimal standards of care for pediatric cancer patients. The best example is the SIOPe (European Society of Pediatric Oncology) guideline, a consensus document describing the minimum quality requirements for a pediatric oncology facility and providing a general directive [83].

In spite of this, and of the existence of several sets of QIs for adult cancer (e.g. for testicular cancer [86]), there is a lack of specific quality standards guidelines and QI systems for childhood cancer. A notable exception to this void is provided by a study of the Pediatric Oncology Group of Ontario (POGO), in which the authors developed a set of QIs for pediatric cancer care [87]. However fruitful the effort is, their proposal is specifically designed for the province of Ontario, Canada, and hence hard to extrapolate to other health care systems such as the different European countries.

Moreover, the management of embryonal CNS tumors is particularly complex due to their aggressiveness and affected organ, the subsequent high severity of illness, the need for multidisciplinary and highly intricate treatments, and the potentially severe immediate and long-term toxicities derived from them. Thus, there is a need for specific QIs for the management of pediatric

brain tumors, against which the overall performance of institutions and networks can be compared.

In this challenging era for public healthcare systems, in which high-quality care is to be provided with limited healthcare resources, we conduct a pragmatic study divided in the three mentioned research projects, in search of areas of improvement in the management of pediatric patients with CNS tumors. We target at three levels: institutional/local, national and European. We hope that our findings will serve as a reference to further develop a quality assurance system with specific QIs for pediatric CNS tumors in the future, and that this will ultimately improve the survival and quality of life of these patients.

5. Context of the research projects

Research Project #1 "Improving the quality of care in the molecular era for children and adolescents with medulloblastoma" is a monocentric, retrospective study performed at Hospital Infantil Universitario Niño Jesús (HNJ), Madrid. This hospital is a reference center for pediatric oncology in Spain, with 100-110 new patients per year (4-6 with medulloblastoma). Oncological multidisciplinary care is provided for pediatric patients from the local region of Madrid and from other parts of Spain.

Research Project #2 "Management and outcome of children and adolescents with non-medulloblastoma CNS embryonal tumors in Spain: Room for improvement in standards of care" is a multi-centric, retrospective study reviewing data from eight major Spanish pediatric oncology hospitals, all of them with one member participating in the CNS Tumors Group of the Spanish Society of Pediatric Hematology and Oncology (SEHOP).

In Spain, there are 46 pediatric oncology units treating children and adolescents with cancer, according to the national childhood cancer registry RETI-SEHOP [88]. However, only 12 centers recruit more than 30 new patients per year [88, 89]. Furthermore, there are approximately five to six new cases of CNS-PNET per year in Spain. Our research project, spanning 10 years, provides data for more than 75% of all cases over that period, as it includes eight major Spanish institutions.

Another aspect to be considered is the persisting inequality across Europe, as pointed out by the Eurocare-5 study [90]. From this international point of view, Spain is unfortunately not among the countries with the highest survival rates, particularly in tumors that require complex multimodal treatments, such as CNS embryonal tumors. Hopefully, our research projects

will contribute to the efforts to improve survival and quality of life of pediatric patients in Spain.

Research Project #3 "Past, present and future of radiotherapy quality assurance in pediatric CNS tumors: A European perspective" aims to have an overall bird view of the situation of RTQA across Europe. Experts from 21 countries provide data for this project, which reflects the heterogeneity and complexity of the European landscape. To better understand the context of this project, the mentioned inequality of outcomes for pediatric cancer patients across Europe should be considered [90, 91], as well as the imbalance in radiotherapy, with a wide range of levels of access to best-care facilities and specialists across European countries [92].

II. HYPOTHESES AND OBJECTIVES

1. AIMS

The broad aim of this study is to analyze the current multimodal management of pediatric patients with central nervous system (CNS) tumors and identify opportunities to improve the quality of care at three levels:

- At a local, mono-centric level, with focus on patients with medulloblastoma (Research Project #1)
- At a national level, with focus on patients with non-medulloblastoma CNS embryonal tumors (formerly called "PNET", primitive neuroectodermal tumors) (Research Project #2)
- At an international, European level, with focus on radiotherapy quality assurance (RTQA) as an essential part of the management of brain tumors (Research Project #3)

The final aim of this work is to identify weak points and propose concrete, pragmatic measures to improve the outcome of children with CNS tumors.

2. HYPOTHESES

- Locally, nationally and internationally, there is a significant gap between clinical trial results and actual patient care and real-world data that can be better understood and reduced within the frame of quality assurance.
- A thorough evaluation and audit of treatment practices and survival outcomes of pediatric patients with embryonal CNS tumors (medulloblastoma and PNET) treated in Spanish hospitals will allow

identifying weak points and improvement opportunities in the management of these patients (Research Projects #1 and #2).

- The development and future implementation of a set of pragmatic measures to tackle the identified weak points in the multimodal treatment of pediatric embryonal tumors in Spain will lead to improved outcomes (Research Projects #1 and #2).

- The review of current and past RTQA practices for pediatric CNS tumors across Europe will help the ongoing construction of international RTQA programs that will further optimize the irradiation treatment, maximizing survival rates and reducing long-term sequelae (Research Project #3).

- The follow-on projects derived from this thesis, including molecular classification with tissue microarrays of the local medulloblastoma cohort; molecular diagnostic re-evaluation with methylation profiling of the Spanish CNS-PNET cohort as part of a world-wide collaboration study and an international survey on the RTQA practices across Europe in collaboration with EORTC will increase institutions' collaboration at a national and international level, and help build strong research networks, which will benefit patients in the mid-term and improve their outcomes.

These hypotheses translate into the following objectives:

3. OBJECTIVES

Research Project #1:

I) To conduct an analysis of treatment strategies and outcomes (toxicity and survival) in a real-world cohort of pediatric patients with medulloblastoma in a Spanish reference pediatric oncology center

II) To identify weak points and to propose a set of quality indicators to implement at a local/institutional level

Research Project #2:

III) To conduct an analysis of treatment strategies and outcomes (toxicity and survival) in a real-world cohort of pediatric patients with CNS-PNET in Spain (multi-centric review)

IV) To identify weak points and improvement opportunities in CNS-PNET to implement at a local and national level.

V) To set the foundations of a collaboration at the ongoing world-wide study for molecular diagnostic re-evaluation with methylation profiling of CNS-PNET (led by the German Cancer Research Center, DKFZ) that will lead to the implementation of the methylation profiles in routine clinical practice

Research Project #3:

VI) To review and analyze past and current practices in RTQA for pediatric patients with brain tumors across Europe (description of national and international RTQA programs and initiatives)

VII) To perform an international survey in an "ask-the-expert" approach to gather information about the current practices of RTQA across Europe, approaching both pediatric neuro-oncologists and radio-oncologists.

III. RESEARCH PROJECT #1:

Improving the quality of care in the molecular era for children and adolescents with medulloblastoma

1. INTRODUCTION

Medulloblastoma is the most common malignant central nervous system (CNS) tumor of childhood, accounting for 20% of all primary CNS tumors among children [6, 93]. It is an aggressive, embryonal tumor that requires multimodal treatment to achieve the current survival rates (global 5-year OS of 56%; 67% for children >4 years) [93, 94]. Gross-total resection (GTR) and receiving radiotherapy as frontline treatment continue to be two of the most important prognostic factors. This gives an idea of the importance of treating children with medulloblastoma in highly specialized centers, and of implementing quality assurance programs to ensure best management of such complex patients.

Another cornerstone is the gained knowledge on biological features of medulloblastoma over the last few years, which has led to the characterization of four molecular subgroups, with distinct histology, genetics, clinical behavior and patient outcomes: sonic hedgehog (SHH), Wingless (WNT), group 3 and group 4 [20–22]. This new knowledge has been incorporated into the most recent 2016 WHO CNS tumor classification [8]. Furthermore, in the current clinical trials, histopathologic and molecular features are being included in the treatment decision algorithms. For instance, in the recently started SIOP-PNET 5 (NCT02066220), patients <16 years within the WNT subgroup are considered to have a better prognostic, and hence are assigned to a new "low risk" category, which will receive treatment reduction.

This new molecular era will allow to better tailor the treatment for each patient, optimizing survival and reducing long-term toxicities. Beyond that, new therapies are emerging, aiming inhibition of molecular targets involved in the pathogenesis of medulloblastoma, especially for the SHH pathway tumors [44, 46].

However, there seems to be a significant delay in the incorporation of molecular advances into daily practice, leaving specially patients treated outside clinical trials behind.

We present a study conducted at Hospital Niño Jesús (HNJ), Madrid, a reference center for pediatric oncology in Spain, with 100-110 new patients per year (4-6 with medulloblastoma). The aim of this study is to present a real-world cohort of children and adolescents with medulloblastoma, to search for weak points in their management that can be improved at a local/institutional level, and to analyze the use of molecular markers and their incorporation into clinical decision making.

2. METHODS

2.1. Patient identification

The experience of one major Spanish pediatric cancer hospital (HNJ) is collected. The hospital's clinical database was queried for all patients with the diagnosis of "medulloblastoma" between 2003 and 2016.

Local institutional approval was granted for the retrospective chart review.

2.2. Eligibility

Inclusion criteria were histologically confirmed diagnosis of CNS-medulloblastoma (according to the 2000, 2007, or 2016 WHO classification depending on the time of diagnosis [7, 8, 95]), age 0-21 years at diagnosis, time of diagnosis between January 2003 and December 2016, and fully available clinical data.

2.3. Record review

In total, 82 variables were collected (in patients with no relapse/progression). Additional 66 variables were collected for each relapse/progression. Data collected included:

- Demographic and baseline information: sex, date of birth, hospital(s) where the patient was diagnosed/received frontline treatment/received salvage treatment if any, personal and family history.
- Diagnostic characteristics: age and symptoms at diagnosis, duration of main symptom, date of diagnosis, size (magnetic resonance imaging, MRI) and location of the primary tumor, extent of disease (M stage, diffuse infiltration, nodules), histology, molecular markers (including beta-catenin, SHH, p53, C-myc, N-myc, and 6-monosomy).

- Frontline treatment:
    - Global treatment strategy
    - Surgery: date and extent of surgical resection, size of tumor rest, management of intracranial hypertension, surgery of metastasis, surgical complications/toxicities, second surgery (type, motivation and outcome).
    - Radiotherapy: start and end dates, modalities, type of fractioning, site, dose (total, posterior fossa, boost, craniospinal irradiation – CSI-), administered percentage of dose, acute toxicity.
    - Chemotherapy: regimen, start and end date, protocol modifications (time-intensity modifications, dose-intensity modifications, agent withdrawal), intrathecal chemotherapy, toxicities that lead to protocol modifications.
    - Autologous hematopoietic stem cell transplantation (aHSCT): date, disease status and comorbidities pre-aHSCT, conditioning regimen, toxicities (first 100 days), disease status post-aHSCT.
    - Novel strategies/drugs (clinical trials, off-label)
    - End of treatment: date and disease status
- Relapse/Progression: for each relapse/progression, date of diagnosis, diagnostic motivation (symptoms vs per imaging per protocol), relapse disease characteristics (location, extension), new histopathology, and all variables detailed in the previous section ("Frontline treatment") were collected.
- Outcome: live and disease status, date of last follow-up/date of death, cause of death, long-term toxicities/sequelae, rehabilitation treatment, palliative care.

Pathology records were reviewed in light of the latest 2016 WHO classification [8]; this nomenclature is used to present the results.

Size and location of primary tumor was assessed by the diagnostic MRI. Size of the primary tumor was measured in three dimensions. Standard Chang M-stage classification was used [15].

Extent of resection was determined from the operative report as well as post-operative MRI. Gross total resection (GTR) was defined as no evidence of enhancing tumor on post-operative imaging. Subtotal resection (STR) was defined as any surgical resection less than GTR. A third designation, "biopsy only", was given to patients whose operative note included that text.

A distinction was made regarding the tumor rest after the first and second-look surgery (if performed as part of the frontline treatment), between <1.5 cm^2 vs ≥ 1.5 cm^2, as measured by MRI. Post-surgical MRI scans were performed within 48 hours of surgery, as internationally defined.

For this analysis, in the absence of comprehensive molecular analysis for most patients, three risk groups were considered: Younger children (age <3 years), standard risk (SR) and high risk (HR). Patients older than 3 years and with any of the following features were assigned to the HR group: tumor rest ≥ 1.5 cm^2, anaplastic histologic subtype, or M+. Patients older than 3 years and with none of these three features were considered to have SR disease.

Radiotherapy (RT) was given at Hospital Gregorio Marañón, Madrid.

Chemotherapy (CT) modifications were defined as time-intensity deviations (delay >1 week between cycles), dose-intensity deviations (>10% dose reduction of CT agents) and/or CT agents withdrawal.

Toxicities were evaluated following the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v.4.03 [96]. Only grade 3-4 toxicities were collected, with the exception of acute RT toxicities (all were collected).

2.4. Statistical analysis

To calculate time intervals, the following definitions were followed:

- The date of diagnosis was considered the date of the diagnostic MRI.
- Time to diagnosis is equivalent to symptom duration.
- Time to surgery: from the date of diagnosis to the date of initial surgery.
- Time to radiotherapy: from the date of surgery to the start date of irradiation therapy (in those patients that received radiotherapy upfront).
- Radiotherapy duration: from the start date to the end date of irradiation treatment.
- Time to chemotherapy: from the end date of radiotherapy to the start date of chemotherapy (in those patients that received radiotherapy upfront without concomitant CT).
- Chemotherapy duration: from the start date to the end date of chemotherapy (last day any CT was administered).
- Frontline treatment duration: from the date of initial surgery to the date of end of treatment (date of last administered therapy, regardless of the modality).
- Time to progression: from the date of diagnosis to the date of radiologic progression.

Endpoint of analysis for all patients was either the date of last follow-up or date of death.

Survival was estimated using the Kaplan-Meier method, and the exact log-rank test was used for comparisons of survival in different groups. Progression free survival (PFS) was calculated as the time from diagnosis to the date of first progression or relapse, or the date of last follow-up. Overall survival (OS) was defined as the time from first diagnosis to death of any cause or the

date of last follow-up. Log-rank test was applied to identify significant prognostic factors for PFS and OS. 95% confidence intervals (CI) were provided. The significance level was fixed for all *P* values under 0.05.

Analysis was performed using the free software R, version 3.4.0. The ability to do multivariate analysis was limited due to the small sample size and was therefore not performed.

3. RESULTS

3.1. Patient demographics and presentation

Sixty-six patients aged 0-21 years with histological diagnosis of medulloblastoma were identified. Eight patients were excluded from this analysis due to incomplete medical records (Figure 1). That yielded 58 eligible patients (40 male, 18 female).

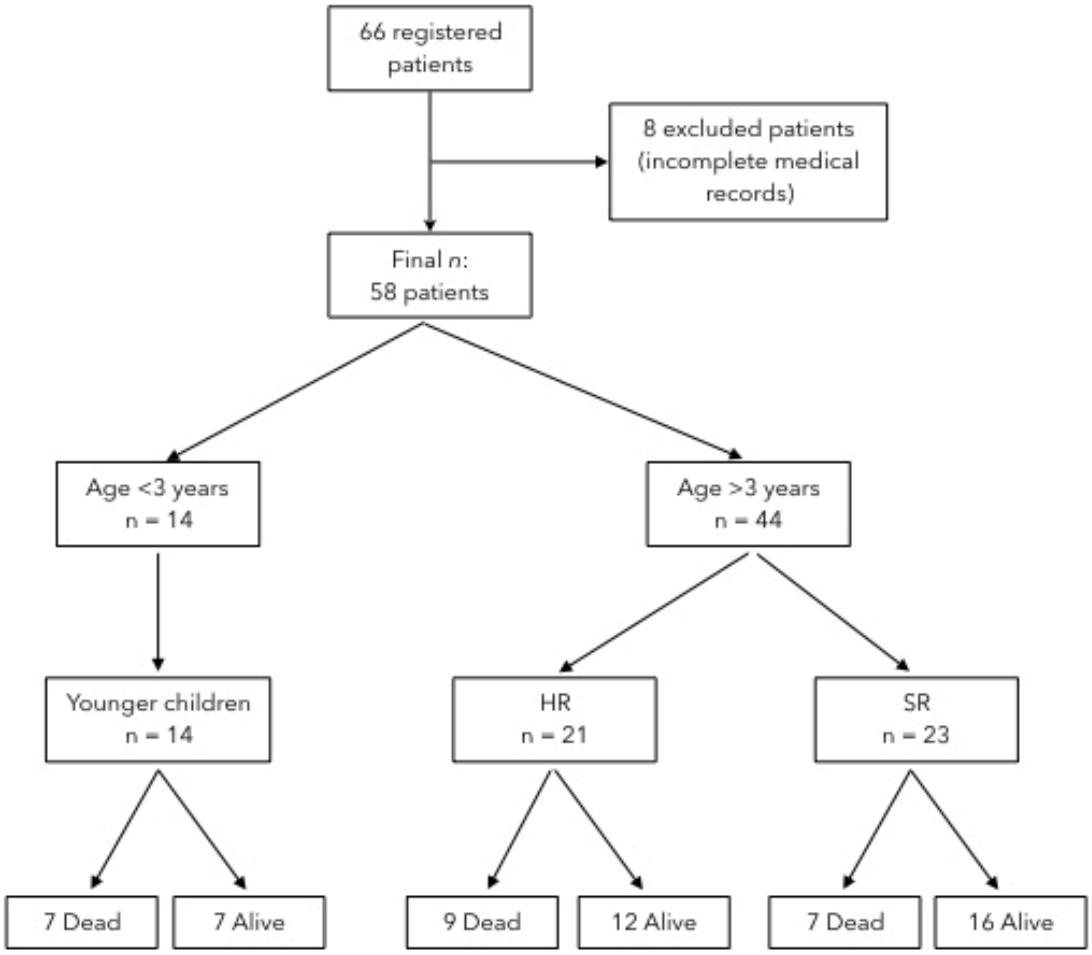


FIGURE 1 Flow diagram of patients. HR: High Risk, SR: Standard Risk

Demographic and diagnosis characteristics are shown in Table 1. The median age at diagnosis was 5.0 years (range 0.6-15.1). One of the patients was diagnosed of Gorlin syndrome after the diagnosis of medulloblastoma [97]. No other patient had relevant medical history or identified genetic disorders.

At presentation, symptoms were heterogeneous, with headache or vomiting occurring in 81% of patients (Table 1), and being the main symptom in 71%. Median duration of the main symptom was 4 weeks (range 0.1-60).

Regarding the diagnostic MRI scan, median longest diameter of primary tumor was 42 mm (range 17.0-77.0). At diagnosis, 19/56 patients (34%) presented with metastatic disease. Three patients were classified as M1 (5%), four as M2 (7%) and 12 as M3 (22%). In two patients, the M status at diagnosis was unknown.

Patient and tumor characteristics	No.	%
Sex	n=58	
Male	40	69
Female	18	31
Age	n=58	
<3 years	14	24
>3 years	44	76
Symptoms at diagnosis	n=58	
Headache	32	55
Vomiting	41	71
Ataxia/Gait impairment	24	41
Neurocognitive symptoms	10	17
Diplopia	8	14
Histology	n=54	
Classic	42	78
Nodular/Desmoplastic	5	9
With extensive nodularity	2	4
Large cell/Anaplastic	3	5
Not otherwise specified (NOS)	2	4
M Chang Stage	n=56	
M0	37	66
M1	3	5
M2	4	7
M3	12	22
M4	0	N/A
Type of metastasis (if M2/M3)	n=16	
Nodules	3	19
Sugar coating	7	44
Both	5	31
Unknown	1	6

TABLE 1 Baseline characteristics

3.2. Biological features

Histologic subtypes according to the WHO 2016 criteria were classic (n=42/54, 78%), nodular/desmoplastic (n=5, 9%), with extensive nodularity (n=2, 4%), large cell/anaplastic (n=3, 5%) and NOS (not otherwise specified) (n=2, 4%). In four patients, the subtype was unknown.

Twenty-four patients were diagnosed with medulloblastoma after 2011 when the four molecular subgroups were defined [21]. However, the determination of molecular markers was not implemented until January 2013 in HNJ Pathology Department. Since then, a national central review panel has been convened, all diagnostic samples are sent to the national coordinating center in Bilbao. From 2013, 19 patients were newly diagnosed, but only eight (42%) have an available complete molecular profile including Beta-catenin, p53, c-Myc, and N-Myc. All markers were negative in all eight cases. Two of the samples were also studied for monosomy 6 (also negative). Additionally, in three samples an isolated Beta-catenin test was performed, one of them with nuclear positivity. Six samples were tested for activation of the SHH pathway, with negative result. The comprehensive four-group classification [21] has not been fully implemented at a national level.

3.3. Referral pathway

The referral path of the patients is reflected in Table 2 and Figure 2. The first line of treatment was administered at Hospital Niño Jesús, Madrid, in 45/58 patients (78%); in four of them, initial surgery was performed in a different institution (but the rest of the first line was completed at HNJ). Three patients (5%) were referred to HNJ for aHSCT. The remaining ten patients (17%) were referred to HNJ after relapse.

Treatment Milestones	Patients	HNJ	Other institutions
Initial diagnostic suspicion (CT or MRI)	n=58	20 (34%)	38 (66%)
First surgery	n=58	41 (71%)	17 (29%)
Frontline treatment (other than surgery)	n=57 *	44 (77%)	13 (23%) **
Any salvage treatment (at least one line of salvage treatment)	n=31	31 (100%)	2 (6%) ***
First salvage treatment	n=31	30 (97%)	1 (3%)
Second salvage treatment	n=13	13 (100%)	0
Third salvage treatment	n=5	3 (60%)	2 (40%)
Fourth salvage treatment	n=3	3 (100%)	0

HNJ: Hospital Niño Jesús, Madrid.

* One patient died due to brain hemorrhage five days after the initial surgery (and thus did not receive any other treatment).
** Three of these patients underwent aHSCT at HNJ as frontline treatment.
*** One patient was treated in two different institutions (other than HNJ) for the first and third salvage lines.

TABLE 2 Treatment center for the different treatment modalities received

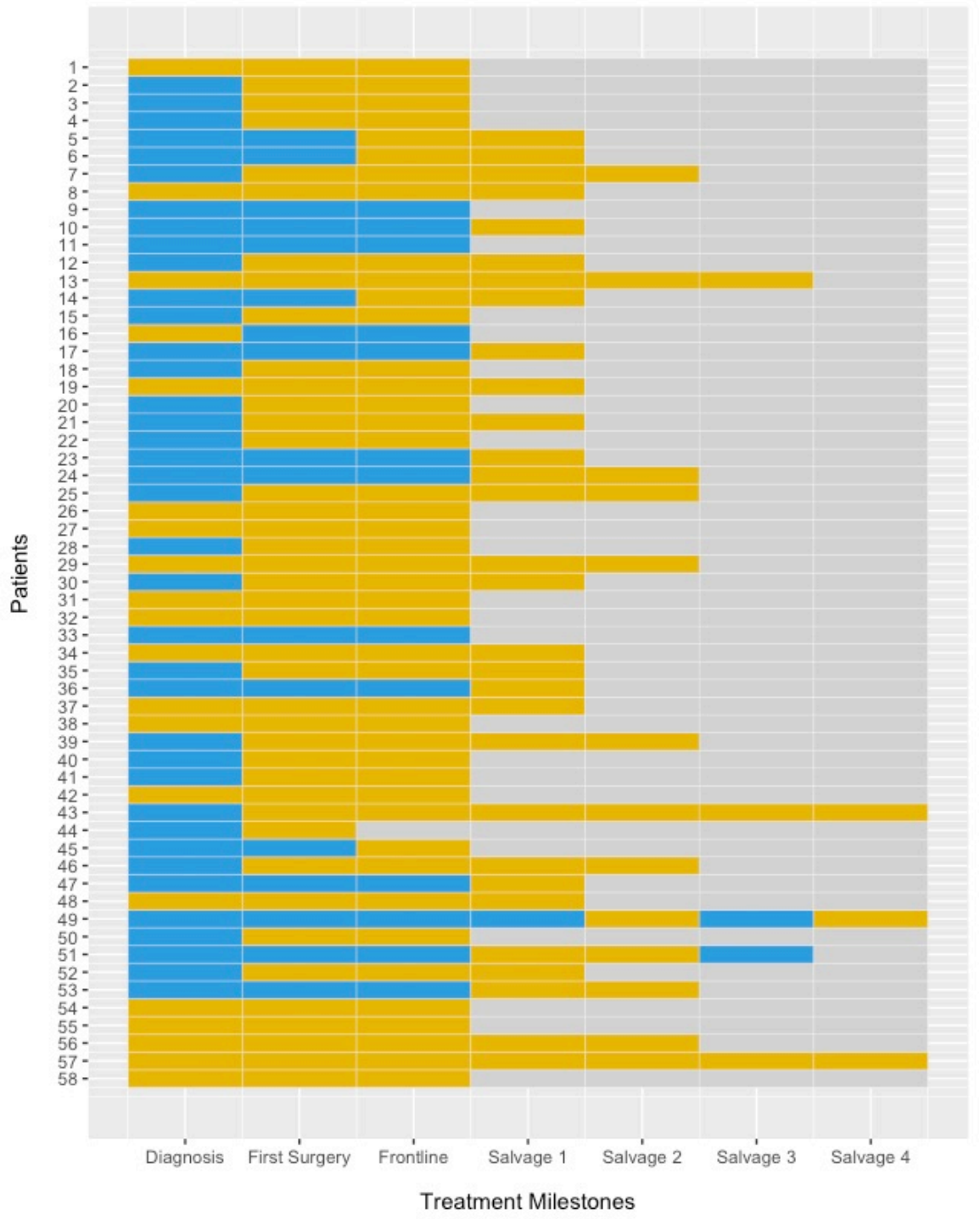


FIGURE 2 Referral pathway. The colors reflect where the treatment milestones occurred: Yellow, Hospital Niño Jesús (HNJ); blue, other institutions; grey, if not applicable (i.e., the patient did not undergo that milestone). Of note: Patients 9, 11 and 33 were referred to HNJ to undergo aHSCT. Note how most patients are diagnosed in other institutions and referred to HNJ for treatment. Note also how most salvage treatments are performed at HNJ, and how most patients, once referred to HNJ, stay there for the rest of treatment milestones.

3.4. First line treatment

3.4.1. Global strategy

Frontline treatment strategy changed over time throughout the years of the study (2003-2016), but was consistent within patients treated at HNJ (Tables 3 and 4). Younger children (<3 years) were treated with radiation-sparing protocols: SFOP (French Society of Pediatric Oncology) [47] from 2003 to June 2005; Head Start II [34] from July 2005 to 2016. Older children (>3 years) and adolescents were treated according to their risk stratification: Standard-Risk patients followed SIOP-PNET 4 [98] from 2003 to 2015, and SIOP-PNET 5 (NCT02066220) since 2016; High-Risk patients were treated following HART-Milan [28] until 2014, and COG-ACNS0332 (NCT00392327) since 2015. In other institutions, patients were treated following different protocols (e.g. Packer, UKCSSG 2001) (Table 4). Three patients were included in the SIOP-PNET 5 trial, which opened at HNJ in 2016. The rest of the patients were treated as "per protocol", as the respective trials were not available at HNJ at that time.

The treatment strategies had a common basis; all of them included surgery with the widest possible resection. Additionally, CSI was administered whenever the patient's age allowed it (patients older than 3 years). Hence, patients were treated upon two main categories, radiation-sparing and radiation-inclusive protocols, depending on their age, with a cut off between 3 and 4 years; the use of radiotherapy on first line applied for older patients, and sparing or delaying radiation for younger patients. Following this classification, 16 patients (27%) were treated with treatment strategies designed to avoid radio-induced brain damage, whereas 41 patients (71%) were treated with radiation-inclusive regimens. (One patient died shortly after surgery). Chemotherapy (CT) was used as consolidation in patients receiving RT upfront, and to delay RT in radiation-sparing protocols. Another extended first-line

modality was aHSCT, with 14 patients (24%) undergoing transplant (nine within radiation-sparing strategies, five within radiation-inclusive strategies).

Frontline treatment	No.	%
Global strategy	n=58	
SIOP-PNET 4 [98]	27	47
SIOP-PNET 5 (NCT02066220)	3	5
HART-Milan [28]	6	10
COG-ACNS0332 (NCT00392327)	2	3.5
SFOP [47]	2	3.5
Head Start II [34]	11	19
Others	7	12
Treatment modalities	n=58	
Surgery	58	100
Gross total resection	34	59
Subtotal resection	21	36
Biopsy only	3	5
Second look	4	7
GTR after second look	1	2
Radiotherapy upfront	41	71
>4 years old	34	59
3-4 years old	7	12
Only local field (focal RT)	0	NA
Local field + CSI	41	71
Hyperfractionated RT	6	10
No RT upfront	17	29
Chemotherapy		
Systemic CT	57	98
Intrathecal CT	8	14
aHSCT	14	24
No CT upfront	1	2

aHSCT: Autologous Hematopoietic Stem Cell Transplantation; CSI: Craniospinal irradiation; CT: Chemotherapy; GTR: Gross total resection; NA: Not applicable; RT: Radiotherapy.

TABLE 3 Frontline treatment characteristics

Treatment Milestones	Younger Children n=14	High Risk n=21	Standard Risk n=23
Global strategy	SFOP Head Start II	HART-Milan COG-ACNS0332	SIOP-PNET 4 SIOP-PNET 5
GTR	6 (43%)	8 (38%)	21 (91%)
Radiotherapy	0	19 (90%)	22 (96%)
aHSCT	9 (64%)	5 (24%)	0
Live status	Dead 7 (50%) Alive 7 (50%)	Dead 9 (43%) Alive 12 (57%)	Dead 7 (30%) Alive 16 (70%)

aHSCT: Autologous Hematopoietic Stem Cell Transplantation; GTR: Gross total resection.

TABLE 4 Frontline treatment characteristics according to risk groups

3.4.2. Surgery

All patients underwent surgery on the first-line approach. Median time to surgery (from MRI diagnosis) was four days (range 0-64). Among patients who underwent initial surgery at HNJ (n=41), median time from diagnosis to surgery was four days (range 2-28) for those diagnosed at HNJ (n=19) versus four days (range 1-64) for those diagnosed at other institutions (n=22). For patients that underwent initial surgery at other institutions (n=17), median time to surgery was two days (range 0-43).

GTR was accomplished on first surgery in 34/58 patients (59%) and on second-look surgery in one patient (2%). In 20 patients (34%) only STR was achieved, despite three of them undergoing a second-look surgery.

Forty-three patients (n=54, 80%; 4 unknown) showed grade 3-4 severe surgical complications: cranial nerves paresis/paralysis (n=17/54, 31%), mutism/posterior fossa syndrome (n=14, 26%), infection (n=13, 24%). One

patient underwent second surgery for ventriculoperitoneal shunt repair. One patient died five days after surgery due to massive tumor hemorrhage, while three other patients survived brain hemorrhage after surgery (without second surgery).

3.4.3. Radiotherapy

RT was administered to 41 patients (n=58, 71%) as frontline treatment, all of them with CSI. Indeed, all children aged 4 and above received CSI as part of frontline treatment, excepting the one that died due to surgical complications. Between 3 and 4 years of age, most patients received CSI as well, with the exception of two patients (3.1 and 3.2 years) who did not receive RT on first line, undergoing radiation-sparing treatment protocols instead.

For 31 patients that received RT right after surgery, median time from surgery to RT start was 39 days (range 3-127). The patient receiving RT three days after surgery underwent only a biopsy and was in a critical neurological condition.

Median dose to the posterior fossa was 54 Gy (range 54.0-68.0), while median CSI dose was 23.4 Gy (range 23.4-39.8). In two patients, 8 Gy were also administered as a boost to the tumor bed.

Median duration of RT was 43 days (range 30-75). Most patients (n=14/26, 54%; 15 unknown) presented acute toxicity (first three months after RT start date), which consisted mainly of grade 1-2 radiodermatitis (n=7/14, 50% of patients with toxicity), grade 2-3 gastrointestinal toxicities (dysphagia, mucositis, vomiting) (n=6, 43%). Two patients had grade 4 pancytopenia, and one had a grade 4 disseminated infection caused by herpes simplex virus 1 and varicella-zoster virus.

3.4.4. Chemotherapy

All patients but one received CT as part of their first line treatment (n=57/58, 98%). The patient not receiving CT was the one deceased after surgery. When combined with irradiation (n=41), CT was administered as consolidation after RT in 33 (80%) patients, and prior to RT (or as a "sandwich") in eight (20%) patients.

Intrathecal CT was used in 14% of the patients (n=8/58) as part of frontline treatment, mostly in younger children (<4 years), and it was mainly based on intrathecal cytarabine (5 patients) and intrathecal liposomal cytarabine (3 patients).

Median duration of systemic CT treatment was 6.2 months (range 1.5-19.0). For patients receiving conventional Packer chemotherapy (i.e. patients treated following SIOP-PNET 4), median duration of CT was 10.0 months (range 1.5-13.3). Of note: the median duration is lower than the theoretical Packer regimen duration (10.3 months) because almost half of the patients (13/27, 48%) did not complete the eight foreseen cycles (due to toxicities and/or disease progression). Up to 63% of patients (n=34/54, 4 unknown) required significant modifications on the original CT plan due to chemotherapy-related toxicities. Forty-two percent (n=22/53, 5 unknown) had time-intensity modifications, with at least one significant delay on a CT-cycle start. Twenty-six percent (n=14/53, 4 unknown) had dose-intensity modifications, with at least one CT agent dose reduction (at least 10% over initial dose). In 28% (n=15/53) of the patients at least one CT agent had to be withdrawn or substituted with another agent (e.g. cisplatin substituted for carboplatin due to tubulopathy or ototoxicity).

3.4.5. Autologous HSCT

aHSCT was performed as part of the first-line strategy on 14 patients (24%), in five (36%) of them in combination with irradiation. It followed RT as consolidation treatment in all five of them. Only one of them underwent a double tandem transplantation (n=1/14, 7%). Patients were on situation of complete response (n=8, 57%) or partial response (n=6, 43%) prior to starting aHSCT. One of the patients went from partial response to complete response after aHSCT, one went from partial response to progressive disease, and the rest had the same disease status after aHSCT. Eight patients (57%) had grade 3-4 post-HSCT toxicities aside from hematologic toxicities, including mucositis, engraftment syndrome, bacteremia, and varicella-zoster infection. One patient treated following the HART-Milan protocol developed tetraparesis and need for mechanical ventilation after receiving thiotepa as conditioning regimen after radiotherapy.

3.5. Toxic mortality and second malignancies

One patient (2%) died due to toxicity, five days after surgery (massive tumor bleeding). No patients died due to CT or acute RT toxicity. During follow-up, four patients (7%) developed second malignancies: Two patients developed myelodysplastic syndrome, one of them dying 4.4 years after the diagnosis of medulloblastoma due to septic shock in the context of the myelodysplasia (the same patient that suffered from tetraparesis after the use of thiotepa, mentioned above); one patient developed several basal cell carcinomas over the irradiation zones, and was diagnosed with Gorlin syndrome [97]; and one patient developed a high-grade diffuse astrocytoma, 3.6 years after completing the RT treatment, and started combination therapy with RT and temozolomide.

3.6. Relapse and patterns of failure

Thirty-one (53%) patients experienced relapse. Median time to first relapse was 13.8 months (range 2.4-50.2). Twenty (65%) patients had received RT as frontline treatment.

Thirteen patients (n=58, 22%) had a second relapse, five (9%) a third relapse, and three (5%) a fourth relapse.

First relapse was local in 5/31 patients (16%), metastatic in 15 patients (48.5%), and both local and metastatic in 11 patients (35.5%). From the 26 patients with metastatic relapse, eight patients (30.5%) presented with nodules, nine patients (35%) had diffuse infiltration ("sugar coating"), and eight (30.5%) had both. One patient (4%) had M4 disease, with a bone metastasis.

3.7. Salvage treatment on first relapse

Surgery was used on 10/31 patients (32%): in two patients for ventriculoperitoneal shunt repair/placement; in one patient for biopsy; in one patient to achieve GTR of the relapsed primary tumor (unsuccessfully); and in six patients to remove metastatic nodules. RT was used on 12/31 patients (39%). Five (42%) of them had received RT previously as first line approach and had focal re-irradiation. In 29/31 patients (94%) chemotherapy was used, 16 of them (55%) with diverse irinotecan-temozolomide regimens [99]. Twelve patients (41%) also received intrathecal chemotherapy and another three underwent aHSCT. Only two patients (n=31, 6%) were enrolled in early phase clinical trials and received novel agents: a first-in-child trial of Celyvir (NCT01844661) and a phase II study of irinotecan in combination with temozolomide [99]). There are 10 survivors (32%) among the relapsed patients, with a median follow-up of 5.8 years (range 2.2-10.9). At initial diagnosis, five of them (50%) had been classified as HR, three (30%) as SR, and two of them (20%) were younger children (<3 years).

3.8. Outcomes and prognostic factors

Median follow-up for survivors was 5.2 years (range 0.7-13.0). See figure 3 with a swimmer survival plot representing the study population.

For the whole population, 3-year and 5-year PFS were 43% (95%CI 32-59%) and 37% (95%CI 25-53%), respectively. Three-year and 5-year OS were 68% (95%CI 57-82%) and 59% (95%CI 47-75%), as shown in figure 4.

By risk group, 5-year PFS were 28% (95%CI 11-71%) for younger children (<3 years), 25% (95%CI 11-57%) for HR patients (>3 years), and 52% (95%CI 33-79%) for SR patients (>3 years). Five-year OS were 44% (95%CI 23-84%), 51% (95%CI 32-81%), and 77% (95%CI 61-97%), respectively (see figure 5).

Metastatic disease at diagnosis and not having been irradiated on first line were variables significantly associated with worse outcome in the univariate analysis ($p<0.05$), with impact on both PFS and OS (see Figure 6 and Table 5).

For comparability, outcomes for patients treated at HNJ from initial surgery (n=41) are reported here: 3-year and 5-year PFS were 54% (95%CI 40-72%) and 44% (95%CI 30-64%), respectively. Three-year and 5-year OS were 69% (95%CI 56-85%) and 58% (95%CI 44-76%), as reflected in figure 7. Among these patients, 5-year PFS by risk group were: 25% (95%CI 8-83%) for younger children (<3 years), 30% (95%CI 14-65%) for HR patients (>3 years), and 70% (95%CI 49-100%) for SR patients (>3 years). Five-year OS were 25% (95%CI 8-83%), 50% (95%CI 30-82%), and 87% (95%CI 71-100%), respectively.

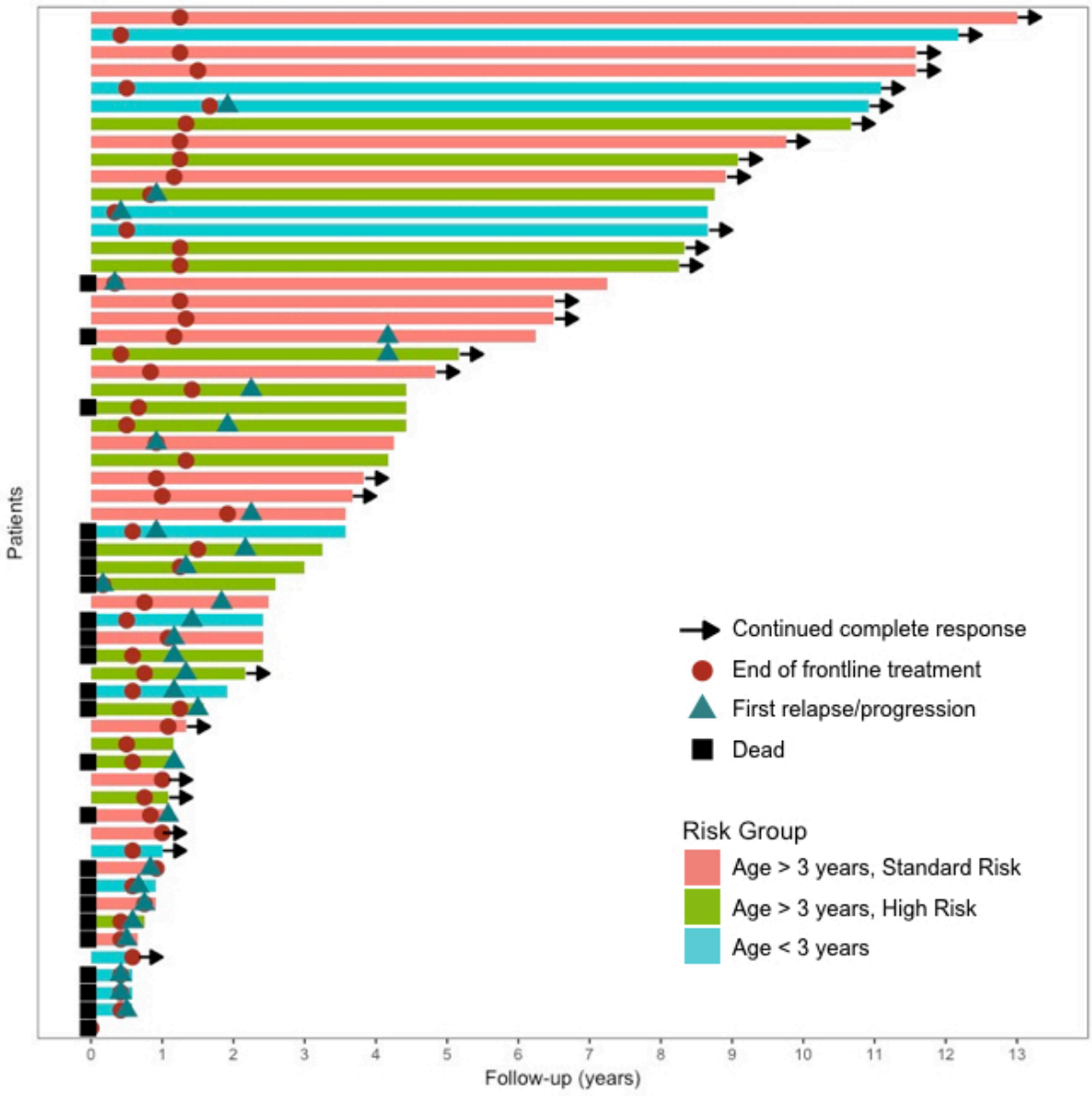


FIGURE 3 Swimmer survival plot for all series.

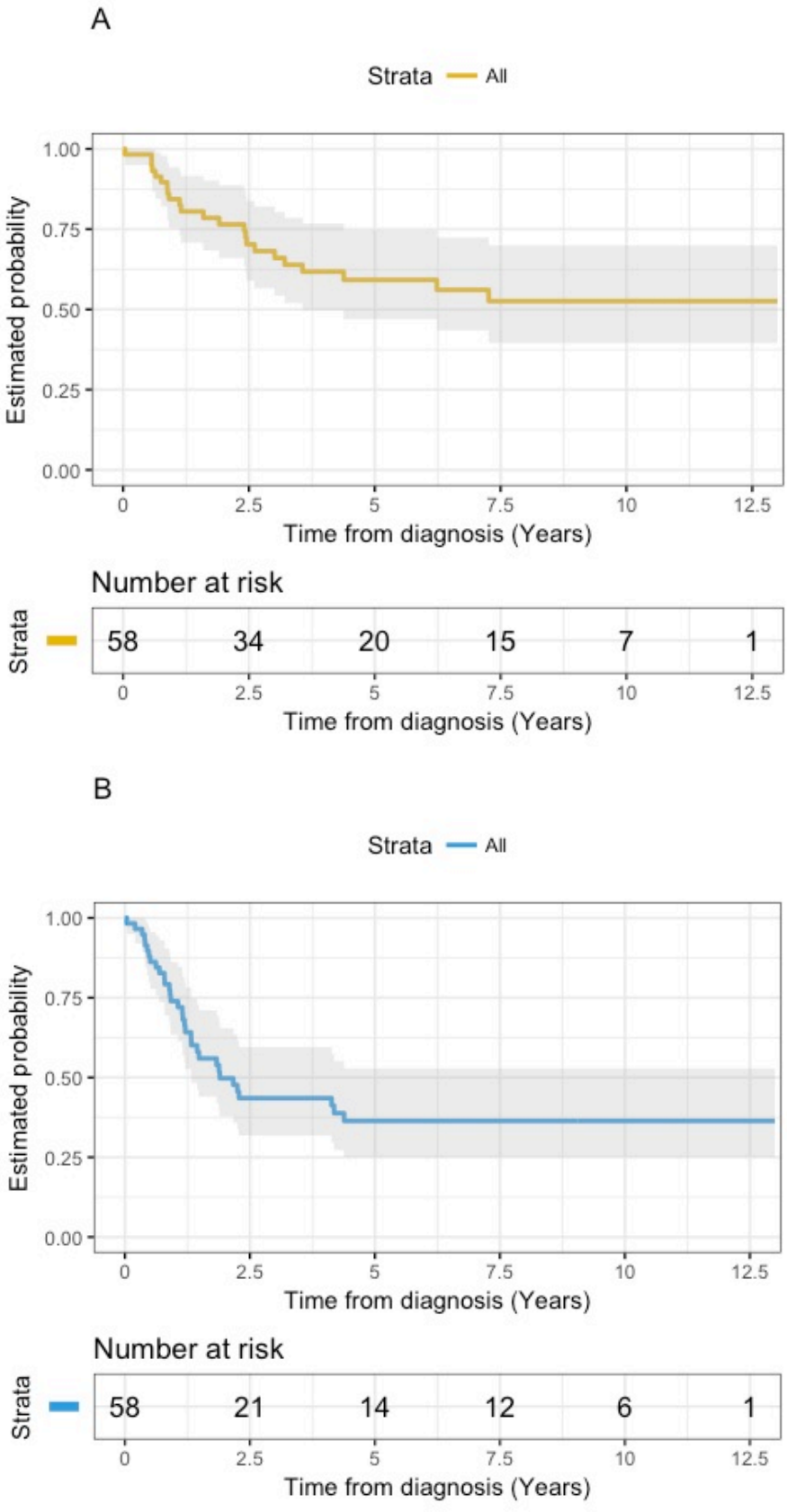


FIGURE 4 Kaplan-Meier Curves for all series. A, Overall Survival. B, Progression Free Survival

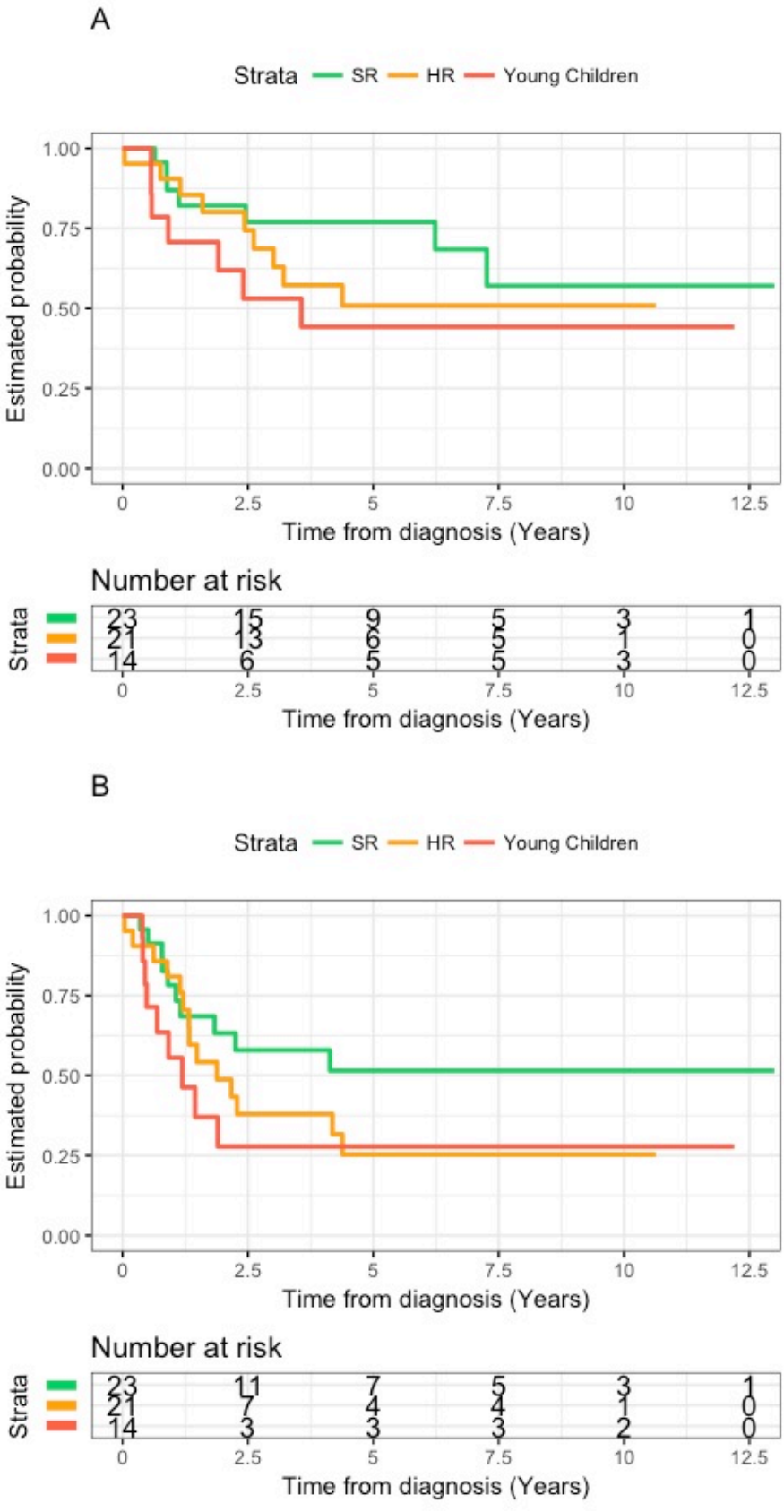


FIGURE 5 Kaplan-Meier Curves according to risk group.

A, Overall Survival. B, Progression Free Survival.

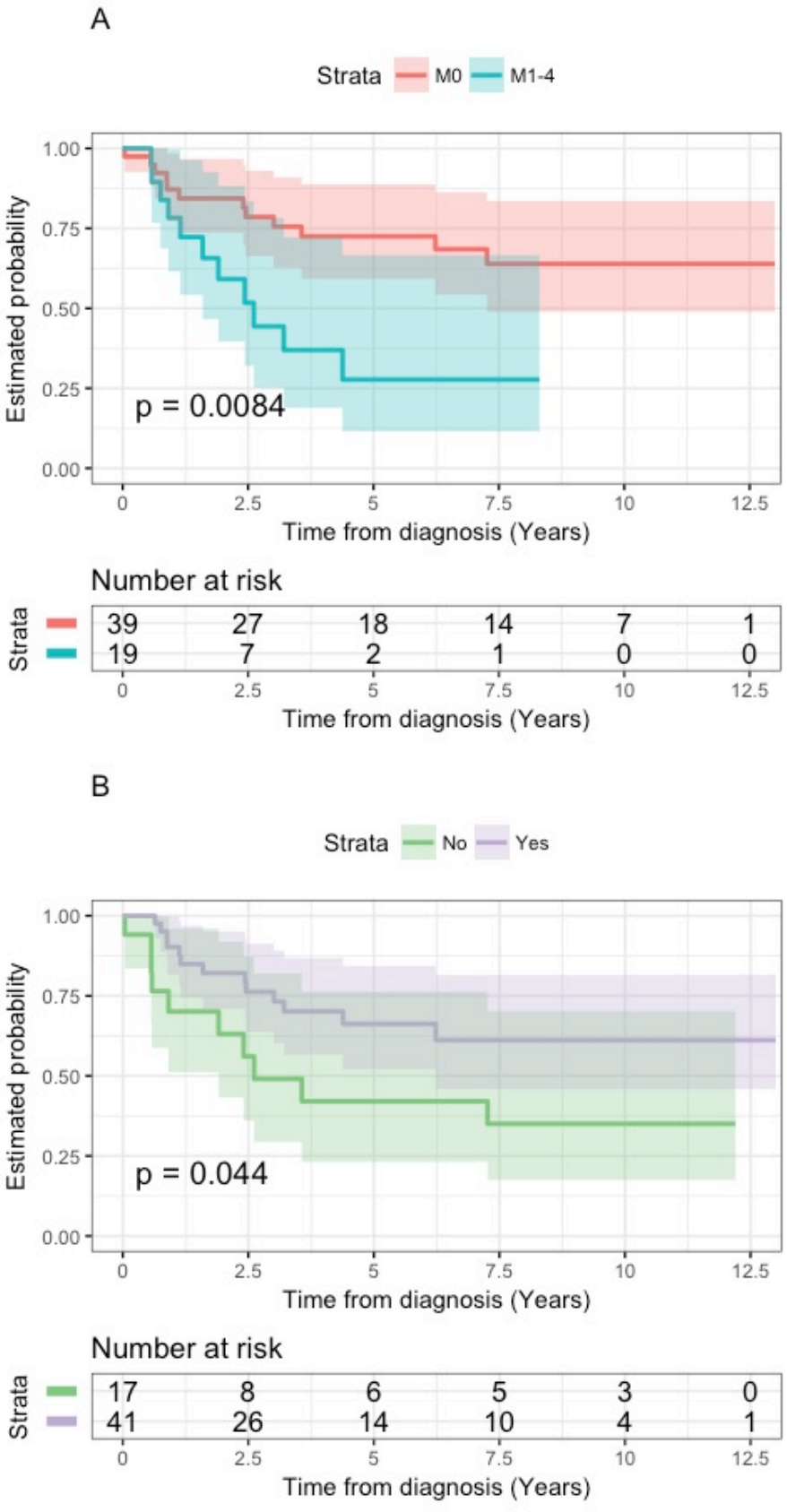


FIGURE 6 Kaplan-Meier Curves for Overall Survival according to disease extension at diagnosis (A) and to radiotherapy as frontline treatment (B).

Variable	5-year PFS (95% CI)	Log-Rank	5-year OS (95% CI)	Log-Rank
Gender (Female vs Male)	17% (5-60%) vs 42% (29-62%)	p = 0.383	45% (23-87%) vs 64% (50-81%)	p = 0.598
Duration of symptoms (≤4 weeks vs >4 weeks)	44% (30-65%) vs 25% (8-74%)	p = 0.354	62% (47-81%) vs 59% (36-95%)	p = 0.552
Age at diagnosis (<3 years vs ≥3 years)	28% (11-71%) vs 39% (26 - 58%)	p = 0.168	44% (23-84%) vs 64% (50-81%)	p = 0.256
Disease extension (M0 vs M1-4)	47% (33-67%) vs 91% (1-55%)	**p = 0.047**	73% (59-89%) vs 28% (12-67%)	**p = 0.008**
Risk Group (SR vs HR and young children)	52% (33-79%) vs 26% (14-48%)	p = 0.111	77% (61- 97%) vs 48% (33-70%)	p = 0.249
Time to surgery (≤4 days vs >4 days	36% (22-58%) vs 39% (21-70%)	p = 0.504	59% (44-79%) vs 57% (38-85%)	p = 0.723
Extent of resection (GTR vs Non-GTR) *	35% (21-58%) vs 38% (21-67%)	p = 0.838	60% (44-81%) vs 58% (40-83%)	p = 0.98
Surgical rest (<1.5 cm vs >1.5 cm)	37% (23-58%) vs 35% (17-69%)	p = 0.637	59% (44-79%) vs 60% (40-89%)	p = 0.869
Radiotherapy (No vs Yes)	23% (9-60%) vs 42% (28-62%)	**p = 0.007**	42% (23-76%) vs 66% (52-84%)	**p = 0.044**
Time to radiotherapy (≤40 days vs >40 days)	56% (36-85%) vs 48% (25-94%)	p = 0.94	73% (54-97%) vs 70% (47-100%)	p = 0.712
CT time-intensity deviations (No vs Yes)	43% (27-70%) vs 34% (19-62%)	p = 0.312	62% (45-86%) vs 52% (35-79%)	p = 0.434
CT dose-intensity deviations (No vs Yes)	38% (25-59%) vs 37% (17-85%)	p = 0.913	60% (45-79%) vs 48% (26-89%)	p = 0.671
Treatment center (HNJ vs Outside HNJ)**	44% (30-64%) vs 16% (4-55%)	p = 0.096	58% (44-76%) vs 65% (44-96%)	p = 0.629

GTR: Gross Total Resection; HNJ: Hospital Niño Jesús; HR: High Risk; OS: Overall Survival; PFS: Progression-Free Survival; SR: Standard Risk.

In bold letters, those comparisons that reach statistical significance (p<0.05).

* GTR achieved after first or second-look surgery

** Patients that underwent frontline treatment from surgery at HNJ (vs those who were referred for only one part of frontline treatment or for salvage therapies)

TABLE 5 Five-year Progression-Free Survival and Overall Survival according to different baseline variables

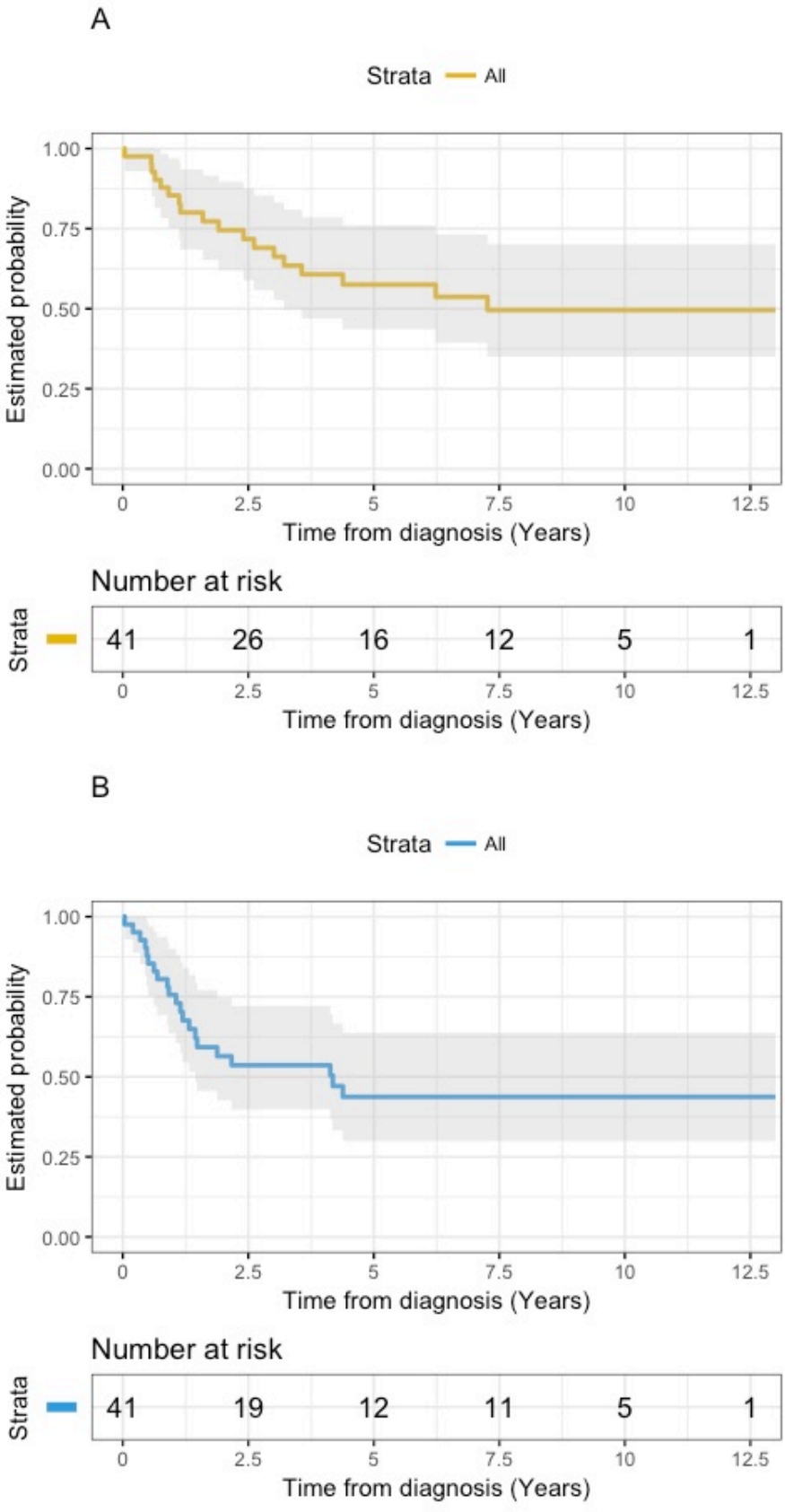


FIGURE 7 Kaplan-Meier Curves for patients treated at HNJ from surgery.

A, Overall Survival. B, Progression Free Survival

3.9. Time-related indicators across different frontline treatment milestones

The timeline measurements were performed as quality indicators of the frontline treatment, as shown in table 6.

Time indicators	Global N (HNJ/Outside)	Global	HNJ	Outside HNJ
Time to diagnosis [weeks] (symptoms duration)	51 (39/12)	4 (0.1-60)	4 (0.1-60)	3.5 (0.7-20)
Time to surgery [days]	57 (41/16)	4 (0-64)	4 (1-64)	1.5 (0-43)
Time to radiotherapy [days]	31 (23/8)	39 (3-127)	36 (3-127)	40.5 (24-73)
Radiotherapy duration [days]	37 (28/9)	43 (30-75)	42 (30-75)	45 (30-58)
Time to chemotherapy [days]	23 (17/6)	42 (7-53)	42 (7-53)	36 (25-48)
Chemotherapy duration [months]	54 (39/15)	6.2 (1.5-19)	7.5 (1.5-15)	4.1 (1.5-19)
Frontline treatment duration [months]	56 (40/16)	9.4 (2.1-19.7)	10.6 (2.1-17.4)	9.0 (3.7-19.7)

HNJ: Hospital Niño Jesús

Patients are divided in two groups: those that underwent frontline treatment from surgery at HNJ versus those that were referred to HNJ for only one part of the frontline treatment or for salvage therapies.
Median and range values (in parentheses) are shown.
The number of patients for which the measurement was done is reflected in the "N" column (taking into account missing values and applicability of each measure).

TABLE 6 Time-related indicators across frontline treatment milestones

3.10. Post-end of treatment toxicities / Sequelae

Grade 3-4 toxicities/sequelae lasting after end of treatment were present in 96% patients (50/52; 5 unknown; one died short after the initial diagnosis). Main toxicities were heterogeneous; they are shown in Table 7.

Neurological toxicities included motor sequelae (paresis/paralysis), cranial nerves palsy, polyneuropathy, ataxia, posterior fossa syndrome, and neurogenic bladder. Neurocognitive sequelae included learning difficulties and IQ loss.

Endocrine toxicities included hypothyroidism, growth hormone deficiency, diabetes insipidus, adrenal insufficiency, malnutrition, and growth failure.

Second malignancies included myelodysplastic syndrome, basal cell carcinomas and high-grade diffuse astrocytoma (described in a previous section).

Other toxicities included epilepsy/seizures, hearing or visual impairment, and renal tubulopathy.

From 2008, the hospital's Palliative Care Unit was created and supported patients with relapsed disease and those with severe disability. Out of the 42 patients diagnosed after its creation, 38% (16/42) were supported by the unit.

Grade 3-4 long-term toxicities	Alive (n=31)	Dead (n=21)
Motor sequelae	16 (52%)	14 (67%)
Other neurological sequelae	17 (55%)	12 (57%)
Endocrine toxicities	13 (42%)	4 (19%)
Neurocognitive sequelae	9 (29%)	3 (14%)
Second malignancies	3 (10%)	1 (5%)
Epilepsy/Seizures	2 (6%)	1 (5%)
Hearing impairment	3 (10%)	0
Visual impairment	0	1 (5%)

TABLE 7 Grade 3-4 long-term toxicities

3.11. Improvement opportunities and quality indicators

The identified areas of improvement in the treatment of children and adolescents with medulloblastoma, and our subsequently proposed quality indicators are described in table 8.

Areas of improvement	Quality Indicators
Diagnosis	
Quick referral after suspicion/diagnosis	- Time to diagnostic MRI - Time to initial surgery
Centralized diagnosis	- % of centrally reviewed samples - % of samples with basic set of molecular markers
Global strategy	
Inclusion in clinical trials	- % of patients enrolled in clinical trials as frontline treatment - % of patients enrolled in clinical trials as salvage treatment

Standardization of treatments	- Number of protocols/strategies followed within the same patient population - Number of patients receiving treatments off-label
Treatment modalities	
Surgical outcome	- % of patients achieving GTR - Number of deaths due to surgical complications
Experience of surgical team	- Number of patients/year - % of GTR after second-look surgery
Rapid access to RT	- Time to RT <40 days (% of patients)
Access to novel RT modalities	- % of patients receiving particle therapy
Treatment delivery	- Protocol deviations - % of patients with CT dose-intensity modifications - % of patients with CT time-intensity modifications
Outcomes	
Survival	- 5-year Overall Survival - 5-year Progression-Free Survival
Toxicity	- Supportive care guidelines - Treatment-related mortality
Long-term and end-of-life care	
Long-term follow-up	- Standardized follow-up assessments - % of patients with grade 3-4 neurocognitive disorders - % of patients with grade 3-4 endocrine disorders
Palliative care	- % of patients receiving support from the local Palliative Care Unit - Time between engagement of the Palliative Care Team and death - % of patients deceased at home

%: Percentage; CT: Chemotherapy; GTR: Gross Total Resection; HNJ: Hospital Niño Jesús; MRI: Magnetic Resonance Imaging; RT: Radiotherapy.

TABLE 8 Areas of improvement

4. DISCUSSION

Despite overall improvement in the outcome of children and adolescents with medulloblastoma over the last decades, mortality and morbidity rates are still unacceptably high, especially in patients with high risk features [93]. On top of the general effort to develop new treatments [43], there is wide room for improvement to deliver high-quality care at a local/institutional level. These pragmatic changes that would improve the management of children with medulloblastoma have a broad range of complexity. For instance, at a European level, there are ongoing initiatives such as QUARTET ("QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials"), which aims to build a radiotherapy quality assurance (RTQA) platform across all pediatric malignancies in Europe in trials [100]. It is constituted in partnership between SIOPe (European Society of Pediatric Oncology) and the EORTC (European Organisation for Research and Treatment of Cancer), and it will help implement RTQA programs in several SIOPe trials including SIOP-PNET 5 (NCT02066220) for medulloblastoma. At a national level, the CNS Tumors Group of the Spanish Society of Pediatric Hematology and Oncology (SEHOP) has recently published a multi-center analysis of the management of non-medulloblastoma CNS embryonal tumors in Spain, pointing out several aspects that could be improved: developing a common treatment strategy, ideally within international collaborative clinical trials, improving referral pathways and reference centers for treatment of complex and rare tumors, maximizing collaboration among pediatric oncology centers, and incorporating new biological markers and the new classification of embryonal CNS tumors [101]. These national and international initiatives are certainly

steps in the right direction, and they will hopefully contribute to improve the outcome of children with medulloblastoma and other complex CNS tumors.

Beyond this, there are several aspects that could be addressed and improved at an institutional/local level. We have conducted this study at Hospital Niño Jesús in Madrid, Spain, a national referral center for pediatric oncology.

Our pragmatic approach to this real-world cohort of children with medulloblastoma has highlighted the strengths and weaknesses in the management of these patients at a local level. The global outcome of the patients seems comparable to the results obtained in Spain and Europe. The 5-year OS for the whole study population is 59% (95%CI 47-75%), which is similar to the most recent European available data for CNS embryonal tumors, with a 5-year OS of 59.0 (95%CI 49-67), and higher than the 5-year OS of 48% (95%CI 33-62) in Spain [6, 88]. (Of note: these data refer to the period 2005-2007 for Europe and 2005-2008 for Spain, and include all embryonal CNS tumors; 5-year OS data for medulloblastoma only might be higher). It is important to point out that 21% of patients underwent frontline treatment at other institutions (different than HNJ) and were referred to HNJ after relapse/progression. This percentage is even higher (29%) if we include patients that were referred to HNJ after initial surgery. Moreover, there are some patients (5%) that only received aHSCT at HNJ. This heterogeneity on referral pathways potentially adds a selection bias, as more high-risk patients tend to be referred as opposed to standard-risk patients.

Other positive remarkable findings are the fact that the treatment strategies are homogeneous within patients receiving frontline treatment at HNJ, which is not always granted among complex tumors treated outside clinical trials [101]; and the fact that the majority of deceased patients (78%) were managed by the local Palliative Care Unit at the end of life. Furthermore,

median time from diagnosis to surgery was four days, and median time from surgery to RT was 39 days, which falls within the international standards of care (40 days) and has proven to be a major prognostic factor [93]. Lastly, only one patient died as a direct treatment-related toxicity (surgical complication).

In spite of the acceptable survival rates and of the positive findings, there are several aspects that could be improved at this institutional level.

1. The retrieval of information from the medical records, mainly in paper format, is difficult due to several factors. The transition to digital records started slowly at HNJ in 2016; in the meantime, and especially for older records, the access to the original paper records can be challenging and adds additional burden to auditing our clinical practice.
2. The retrieval of information about patients referred from other institutions proved to be challenging.
3. There is no systematized database for treated cancer patients at HNJ. This is an important pitfall, especially in a national reference institution that provides oncological care for 100 new patients each year (4-6 of them with medulloblastoma).

   For sure, these limitations accessing medical records as well as missing data hinder the implementation of QA measures and of institutional clinical audits, which could certainly lead to an improvement in the overall management of the patients.
4. Histological diagnosis is provided at the local pathology department, with no central review of the samples. While complex cases are referred to other institutions for review, this is not performed in a systematized way. However, the situation has improved since the

opening of the SIOP-PNET 5 trial at HNJ in 2016, in which pre-treatment central pathology review is mandatory.

5. There is a delay between the advances in the biological knowledge about medulloblastoma and the translation of this knowledge into clinical practice. This is a problem common to other pediatric cancer types and to other rare diseases [102] and is yet to be addressed at leading institutions such as HNJ. While the four molecular medulloblastoma subgroups were formerly defined in 2011 [21], molecular markers were not implemented until January 2013 in the local pathology department. Since then, only 42% of the newly diagnosed patients had an available complete molecular profile. Of note: since 2016, eligible patients at HNJ are included in the clinical trial SIOP-PNET 5, facilitating the implementation of a basic molecular profile for all newly diagnosed patients.
6. The frontline strategy for patients treated at HNJ was homogeneous throughout the risk groups. Nonetheless, few patients were included in the respective clinical trials, while most were treated following the protocols or publications of those trials. Furthermore, among the patients that had relapse/progression, only two (6%) were included in clinical trials and received novel therapies. This will certainly improve over the next years thanks to the growing network of the SEHOP and to the recent set up of the Clinical Trials Unit at HNJ [103], which is part of the ITCC (Innovative Therapies for Children with Cancer) consortium [104].
7. The size of the surgical rest is a well-known prognostic factor. However, in spite of over one third (36%) of the patients not achieving GTR on initial surgery, only four of them (19%) underwent second-look surgery (one of them achieving GTR). Although recent

studies suggest that the prognostic benefit of increased extent of resection is attenuated after molecular subgroup affiliation is taken into account [19], maximum safe surgical resection remains the standard of care.

8. Regarding RT practices in our study population, missing data impaired a more comprehensive review. While it has notably improved over the last five years, this is an area that needs further upgrading. Thorough collection of RT data (including RT plans and imaging) could lead to better reviews of the RT practices and to the implementation of a local RTQA program. Furthermore, equal access to novel RT modalities (e.g. proton therapy, IMRT, gamma knife) should be granted.
9. Almost all patients (96%) are reported to have grade 3-4 long-term toxicities. However, the reporting of toxicities varies among areas. While motor/neurological and endocrine sequelae have a similar reported incidence compared with other series found in the literature, other toxicities such as hearing impairment and neurocognitive sequelae seem underreported [52, 55, 57]. A systematic neurocognitive evaluation program should be implemented to better define and address the needs of the survivors.
10. While the quality of life (QOL) and the patient-reported outcomes (PROs) are gaining increasing importance in the cancer research community over the last decade [105–107], none of the patients included in our study underwent QOL assessment, neither during treatment nor during follow-up. From 2016, this has been improving thanks to the opening of the clinical trial SIOP-PNET 5, which includes

serial QOL assessments; an important step towards the optimization of psychosocial support for these patients.

Some limitations of this study ought to be acknowledged. The retrospective nature of the study has magnified the problem of missing data (addressed in the previous points 1.-3.), making some important information inaccessible (especially regarding RT plans and lines of treatment provided outside HNJ). The lack of central pathology review has to be pointed out as well. The monocentric nature of this work makes the resulting sample size (n=58) inadequate for complex statistical analysis (e.g. multivariate analysis), and hence the conclusions derived from survival analysis should be handled carefully. On the other hand, the main aim of this review is to find aspects in the care of patients with medulloblastoma that can be improved at a local level, and in that regard, this monocentric approach to a referral institution such as HNJ serves its purpose in a very pragmatic way. The identified areas in need of improvement may be extrapolated to other pediatric oncology centers in Spain; nonetheless, a national review and a common strategy should be encouraged. The multidisciplinary team workflow already in place at HNJ, with a smooth and quick collaboration between all the cancer care providers (pediatric oncologists, surgeons, radio-therapists, nurses, psychologists, etc.) and strongly promoted by the weekly tumor board meetings, is a good model to be exported to other national centers.

A further strength of this study is the long-term follow-up of the patients at HNJ; in spite of the majority of them coming from other parts of Spain, the median follow-up time of survivors was longer than five years. Moreover, this study analyses a real-world data cohort which allows to draw conclusions that go beyond those driven from clinical trial cohorts. Hopefully, this study will help to better understand the gap between clinical trials and real-world survival and to find ways to reduce this gap.

The main conclusion of this work is that there is widely room for improvement at an institutional level in the management of children and adolescents with medulloblastoma in Spain. Although the survival rates of children treated at HNJ are comparable to those achieved across Spain and Europe, there are several specific aspects that could be optimized. This study has served to identify several areas of improvement and to propose concrete and affordable measures. The first step could be to implement a quality assurance system; this includes creating a database for the systematic collection of patients' data and performing regular clinical audits. In lack of internationally validated quality indicators for the management of pediatric patients with CNS tumors, the quality indicators proposed in our study may be of help. Other measures that can benefit patients include: maximizing the inclusion of patients in international clinical trials and expanding the Clinical Trials Unit; establishing a central pathology review; accelerating the translation of the new molecular knowledge into daily practice through the use of up-to-date biological markers; and implementing a neurocognitive and QOL evaluation program.

Beyond the local level, there is a strong need for collaboration and networking in the treatment of complex CNS tumors such as medulloblastoma. Single institutions, especially reference centers, will benefit from an enhanced national network and from the implementation of well-structured referral pathways; and vice versa, the national (and European) network would benefit from using a network of institutions with good practices, high quality data and regular auditing of clinical data.

Hopefully, our proposed measures will contribute to the improvement of outcomes for children and adolescents with medulloblastoma in the near future, starting at a local level and beyond.

IV. RESEARCH PROJECT #2:

Management and outcome of children and adolescents with non-medulloblastoma CNS embryonal tumors in Spain: Room for improvement in standards of care

1. INTRODUCTION

Embryonal neuroectodermal tumors of the CNS that are not medulloblastoma, previously called central nervous system primitive neuroectodermal tumors (CNS-PNET) and pineoblastomas (PB) [7, 8], are rare and aggressive embryonal tumors with poor outcome. Together, they account for less than 5% of childhood CNS tumors [2, 6].

Due to their low incidence and to their insufficiently known biology, these tumors have been historically treated with protocols for high-risk medulloblastoma. However, there is growing evidence from molecular genetic studies that CNS-PNET, PB, new entities such as embryonal tumors with multilayered rosettes (ETMR), and medulloblastoma are different entities [59–62]. This knowledge has already been reflected in the most recent 2016 World Health Organization (WHO) classification, that differentiated pineoblastoma from ETMR, C19MC-altered, and has created a "wastebasket" category of CNS embryonal tumors, NOS [8]. There seems to be clinical differences as well, with CNS-PNET/PB showing a more aggressive behavior and lower survival rates than medulloblastoma [73].

Despite the achieved improvement over the last years, the historical series show a 5-year overall survival (OS) of 18-38% [71, 74, 76, 108, 109]. In addition, when practice-changing strategies obtained from clinical trials in particular institutions are brought to general clinical practice, the results, i.e. real-world data, are recurrently disappointing [9].

The two main aims of this study are: to present a tumor-specific, national real-world data cohort (as opposed to clinical trials data) of children and adolescents with CNS-PNET/PB and to identify weak points and quality indicators that can be implemented to improve the still dismal outcome of these patients.

2. METHODS

2.1. Patient identification

Major Spanish pediatric cancer hospitals, all of them with one member participating in the CNS Tumors Group of the Spanish Society of Pediatric Hematology and Oncology (SEHOP), were contacted. At each site, the hospital's clinical database was queried for all patients with the diagnosis of "PNET", "pineoblastoma", "ependymoblastoma" and "Embryonal Tumor with Abundant Neuropil and True Rosettes" (ETANTR) between 2005 and 2014.
(Note: At the beginning of data inclusion, the old terminology "PNET" was being used. Subsequently, the new 2016 WHO classification was published, removing the term ¨PNET" and reclassifying those tumors into the subtypes "ETMR, C19MC-altered", "ETMR, NOS", "Medulloepithelioma", "CNS neuroblastoma", "CNS ganglioneuroblastoma", and "CNS embryonal tumor, NOS" [8]. The old terminology was used for this study.)

The Clinical Research Ethics Committee from Hospital Niño Jesús centrally approved the study. Local institutional approval for retrospective chart review was sought at all participating hospitals.

2.2. Eligibility

Inclusion criteria were histologically confirmed diagnosis of CNS-PNET/PB (according to the 2007 WHO classification [7]), ependymoblastoma and ETANTR, age 0-21 years at diagnosis, time of diagnosis between January 2005 and December 2014, and fully available clinical data. For this study, available pathology reports were reviewed by an experienced neuro-pathologist.

2.3. Record review

Data collected included demographic information, age and symptoms at diagnosis, extent of disease, extent of surgical resection, initial treatment strategy and its deviations and toxicities, as well as information regarding relapses and salvage treatments, if any, and outcome.

Size and location of primary tumor was assessed by the diagnostic MRI. Size of the primary tumor was measured in three dimensions. Standard Chang M-stage classification as established for medulloblastoma was used. [15].

Extent of resection was determined from the operative report as well as post-operative MRI. Gross total resection (GTR) was defined as no evidence of enhancing tumor on post-operative imaging. Subtotal resection (STR) was defined as any surgical resection less than GTR. A third designation, "biopsy only", was given to patients whose operative note included that text.

Chemotherapy (CT) modifications were defined as time-intensity deviations (delay >1 week between cycles), dose-intensity deviations (>10% dose reduction of CT agents) and/or CT agents withdrawal.

Toxicities were evaluated following the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v.4.03 [96].

Patients were stratified regarding whether they received radiotherapy as first-line non-surgical treatment (radiation-inclusive strategies), as opposed to those who followed radiation-sparing baby-brain strategies.

2.4. Statistical analysis

Time to progression was calculated from the date of first treatment to the date of radiologic progression. Endpoint of analysis for all patients was either the date of last follow-up or date of death.

Survival was estimated using the Kaplan-Meier method, and exact log-rank test was used for comparisons of survival in different groups. Progression

free survival (PFS) was defined as the date of first treatment to date of first progression or relapse, or the date of last follow-up. Overall survival (OS) was defined as the date of first treatment to death of any cause or the date of last follow-up. Log-rank test was applied to identify significant prognostic factors for PFS and OS. 95% confidence intervals (CI) were provided. The significance level was fixed for all *P* values under 0.05. Analysis was performed using the SPSS software®, version 21.0, and the free software R, version 3.4.0. The ability to do multivariate analysis was limited due to the small sample size and was therefore not performed.

3. RESULTS

3.1. Patient demographics and presentation

Eight major institutions (out of all nine contacted, belonging to the CNS tumors group of the SEHOP) contributed to this study and included all their potential patients: 52 patients aged 0-21 years with local histological diagnosis of CNS-PNET/PB were registered. Nine patients were excluded from this analysis: three patients who did not meet all inclusion criteria on central review and six patients whose medical records were incomplete (Fig. 1).

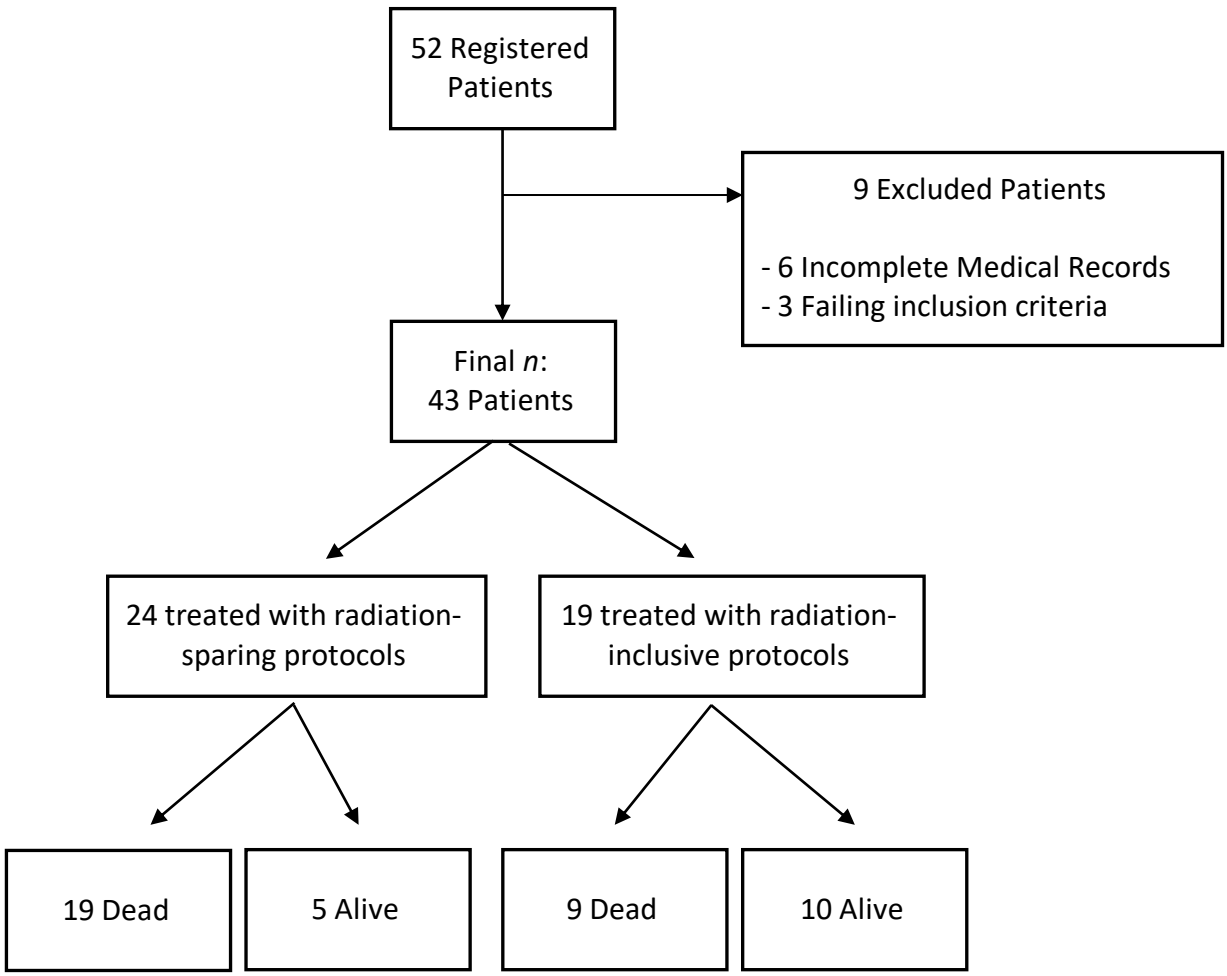


FIGURE 1 Flow diagram of patients

That yielded 43 eligible patients (22 male, 21 female). Demographic and diagnosis characteristics are shown in Table 1. The median age at diagnosis was 3.6 years (range 0.01-14.70). None of the patients had relevant medical history or identified genetic disorders.

At presentation, symptoms were heterogeneous, with headache, vomiting or irritability/somnolence occurring in >81% of patients (Table 1). Median duration of the main symptom was 2 weeks (range 0-12).

Median longest diameter of primary tumor was 60.5 mm (range 21.0-95.0).

At diagnosis, 12 patients (28%) presented with metastatic disease. One patient was classified as M1 (2%), six as M2 (14%) and five as M3 (12%).

3.2. Biological features

Histology was pineoblastoma (n=4, 9%), ependymoblastoma (n=2, 5%), ETANTR (n=3, 7%), ganglioneuroblastoma (n=1, 2%) and PNET (n=33, 77%). Full pathology reports were reviewed in light of the 2007 WHO criteria for 36 patients (84%). 28 cases (78% of those with available pathology report) had all required information to confirm the diagnosis of CNS-PNET and eight cases (22%) had insufficient descriptive information to confirm the diagnosis of CNS-PNET.

As a result of this study, a subsequent retrospective molecular analysis of archival tumor samples available for this patient cohort (22/43, 51%) has been started in collaboration with European reference centers. The preliminary results of the DNA methylation profiling suggest that 55% (12/22) samples were misdiagnosed as CNS-PNET: three medulloblastomas, two glioblastomas, an ATRT, an Ewing sarcoma, a ganglioglioma, a glioma of uncertain malignancy, an ependymoma, a central neurocytoma, and one undetermined.

Characteristics	No.	%
Patient and tumor characteristics		
Sex		
Male	22	51
Female	21	49
Age		
<3 years	16	37
>3 years	27	63
Histology		
CNS-PNET	33	77
Pineoblastoma	4	9
Ependymoblastoma	2	5
ETANTR	3	7
Ganglioneuroblastoma	1	2
M Chang Stage		
M0	31	72
M1	1	2
M2	6	14
M3	5	12
M4	0	N/A
Symptoms at diagnosis		
Headache	25	58
Vomiting	22	51
Neurocognitive symptoms	15	35
Frontline treatment		
Global strategy		
Head Start II [34]	8	19
PNET 4 [98]	5	12
HART-Milan [28]	3	7
COG-ACNS 0334 [NCT00336024]	3	7
HIT (<3 years old) [71]	2	5
St Jude MBL 96	2	5
Others	20	47
Treatment modalities		

Surgery	43	100
Gross total resection	23	53.5
Subtotal resection	7	16.5
Biopsy only	13	30
Radiotherapy upfront	19	44
>4 years old	16	37
3-4 years old	3	7
Only local field (focal RT)	1	2
Local field + CSI	18	42
No RT upfront	24	56
Chemotherapy		
Systemic CT	37	86
Intrathecal CT	8	23
aHSCT	14	33
No CT upfront	6	14

aHSCT: Autologous Hematopoietic Stem Cell Transplantation; CNS-PNET: Central Nervous System Primitive Neuroectodermal Tumors; ETANTR: Embryonal Tumor with Abundant Neuropil and True Rosettes; CSI: Craniospinal irradiation; CT: Chemotherapy; RT: Radiotherapy.

TABLE 1 Baseline and frontline treatment characteristics

3.3. First line treatment

3.3.1. Global strategy

Frontline treatment strategy was very heterogeneous with 17 different approaches. The most frequently used protocols were Head Start II (n=8, 19%), SIOP-PNET 4 (n=5, 12%) and HART-MILAN (n=3, 7%), all of them originally designed for patients with medulloblastoma [28, 34, 98, 110, 111]. In spite of this disparity of strategies, all of them included surgery with the widest possible resection and craniospinal irradiation (CSI) whenever the patient's age and condition allowed it. Patients were treated upon two main categories, radiation-sparing and radiation-inclusive protocols, depending on their age, with a cut off between 3 and 4 years; the use of radiotherapy (RT) on first line applied for older patients, and sparing or delaying radiation for younger patients. Following this classification, 24 patients (56%) were treated with treatment strategies designed to avoid radio-induced brain damage, whereas 19 patients (44%) were treated with radiation-inclusive regimens.

The most important differences in treatment strategies were found among chemotherapy regimens, especially on their drug doses and time-design. Another extended first-line modality was aHSCT, with up to a third of patients (n=14, 33%) undergoing transplant (eight within radiation-sparing strategies, six within radiation-inclusive strategies).

3.3.2. Surgery

All patients underwent surgery on the first-line approach. Median time to surgery (from MRI diagnosis) was three days (range 0-36). GTR was accomplished on first surgery in 19 patients (n=43, 44%) and on second-look surgery in four patients (n=43, 9.5%). In seven patients (16.5%) only STR was achieved, despite five of them undergoing a second-look surgery.

Twenty patients (47%) showed grade 3-4 severe surgical complications: cranial nerves paresis/paralysis (n=7, 16.5%), other motor symptoms such as hemiparesis, limb weakness or hypotonia (n=11, 26%), infection (n=2, 5%). Five patients (12%) underwent second surgery due to complications derived from the first one. Two patients (5%) died due to brain hemorrhage during the second surgery, both performed as a second-look attempt; both patients were neonates.

3.3.3. Radiotherapy

RT was administered to 19 patients (n=43, 44%) as frontline treatment. Four children older than 4 years did not receive RT on first line: in one patient, due to his palliative situation; in the other three, due to radiation-sparing treatment protocols (Head Start II [34] and COG-ACNS0334 -NCT00336024-). Median total dose was 55.8 Gy (range 54.0-62.0). Median CSI dose was 23.4 Gy (range 22.4-39.7) and median dose of the boost to the primary tumor was 26.5 Gy (range 18.0-32.4). One of the patients (8-year-old) received focal RT without CSI. Median duration of RT was 43 days (range 32-59). Most patients (n=12, 63%) presented acute toxicity (first three months after RT start date), but this consisted mainly of grade 1-2 radiodermatitis (n=8, 67% of patients with toxicity). Three patients had grade 3 toxicities (pancytopenia, vomiting). All patients completed the full planned radiation dose.

3.3.4. Chemotherapy

Most patients received CT as part of their first line treatment (n=37, 86%). When combined with irradiation (n=18), CT was administered as consolidation after RT in 12 (67%) patients, and prior to RT in six (33%) patients. Intrathecal CT was used in 23% of the patients (n=8/35). Median duration of CT treatment was 4.3 months (range 0.1-14.5). Up to 63% of patients (n=22/35, 2

unknown) required significant modifications on the original CT plan due to chemotherapy-related toxicities. Forty-nine percent (n=17/35) had time-intensity modifications, with at least one significant delay on a CT-cycle start. Twenty-six percent (n=9) had dose-intensity modifications, with at least one CT agent dose reduction (min. 20% over initial dose). In 23% (n=8) of the patients at least one CT agent had to be withdrawn or substituted with another agent (e.g. carboplatin for cisplatin due to tubulopathy).

3.3.5. Autologous HSCT

Autologous HSCT was performed as part of the first-line strategy on 14 patients (33%), in five (35%) of them in combination with irradiation. It followed RT as consolidation treatment in three (21%) patients, and was administered prior to irradiation in two (14%). Most of them underwent a triple or quadruple tandem transplantation (n=11/14, 79%) [112]. Patients were on situation of complete response (n=7, 50%) or partial response (n=7, 50%) prior to starting aHSCT. One of the patients went from partial response to complete response after aHSCT, one went from partial response to progressive disease, and the rest had the same disease status after aHSCT. Nine patients (64%) had grade 3-4 post-HSCT toxicities aside from hematologic toxicities.

3.4. Toxic mortality

Two patients (5%) died due to toxicity, both during surgery. No patients died due to CT or RT toxicity. During follow-up, no patients developed second malignancies or died of therapy-related causes after completion of treatment.

3.5. Relapse and patterns of failure

Twenty-eight (65%) patients experienced relapse. Median time to first relapse was 6.7 months (range 2.3-44.9). Nine (32%) patients had received RT as frontline treatment.

Eight patients (n=43, 19%) had a second relapse and three (7%) a third relapse.

First relapse was local in 14/28 patients (50%), metastatic in eight patients (29%), and both local and metastatic in six patients (21%).

3.6. Salvage treatment on first relapse

Surgery was used on 13/28 patients (46%), but only in 4/13 patients (31%) GTR was achieved (one of them needing second-look surgery). RT was used on 10/28 patients (36%). Only one of them had received RT previously as first line approach and had re-irradiation. 15/28 patients (54%) were treated with chemotherapy, nine of them (60%) with diverse irinotecan-temozolomide regimens [99] and two with metronomic regimens [113]. Two patients also received intrathecal chemotherapy and another two underwent aHSCT. Only one patient (n=28, 4%) received novel agents (bevacizumab and rapamycin), both used off-label. There are three survivors among the relapsed patients, with a follow-up of 1.8, 2.4 and 3.5 years. The first two patients had local relapse; both underwent surgery, achieving GTR. The third patient presented both with local and metastatic relapse (M2); he did not undergo surgical resection. All three received first RT at the time of salvage therapy, and all three received adjuvant chemotherapy as well.

3.7. Outcomes and prognostic factors

Median follow-up for survivors was 3.5 years (range 1.7-9.3). See Figure 2 with a swimmer survival plot representing the study population.

For the whole population, 3-year PFS was 31.9% (95%CI 17-47%) and 3-year OS was 35.1% (95%CI 20-50%), as shown in Fig. 3.

Age less than 3 years at diagnosis, not achieving GTR and not having been irradiated in first line were variables significantly associated with worse outcome in the univariate analysis ($p<0.05$), with impact on both PFS and OS (Table 2).

3.8. Neurocognitive outcome

The study did not include routine neurocognitive assessments due to its retrospective nature and hence, these toxicities are likely under-reported.

Grade 3-4 long-term neurocoginitive toxicities/sequelae were present in 11/15 (73%) survivors, all of them needing intensive physical and neurocognitive rehabilitation treatment. These moderate-severe sequelae included hearing (27%) and visual impairment (20%), learning difficulties and/or IQ loss (27%), epilepsy (20%) and other neurological deficits, e.g. neuropathy (33%).

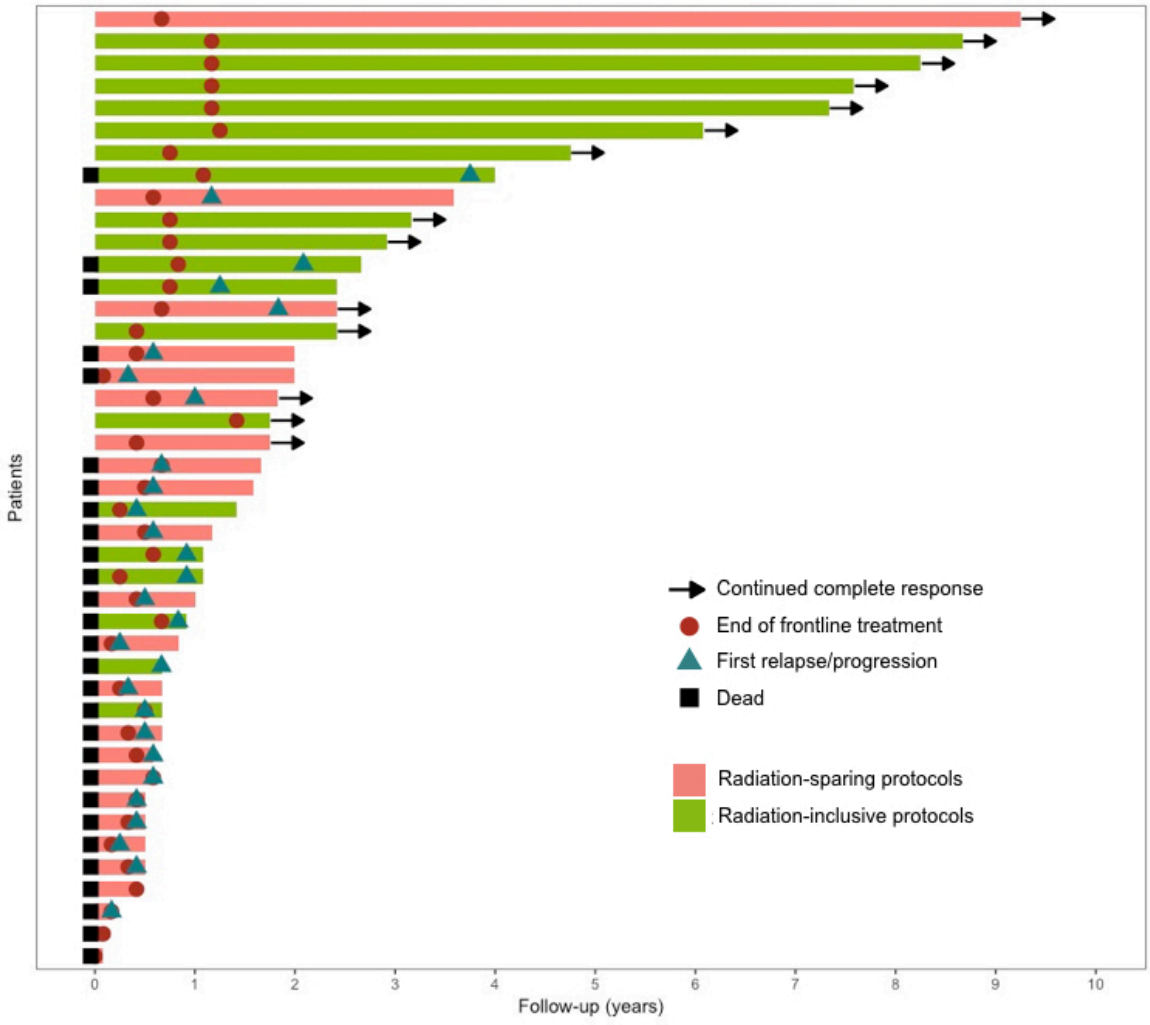


FIGURE 3 Swimmer survival plot for all series.

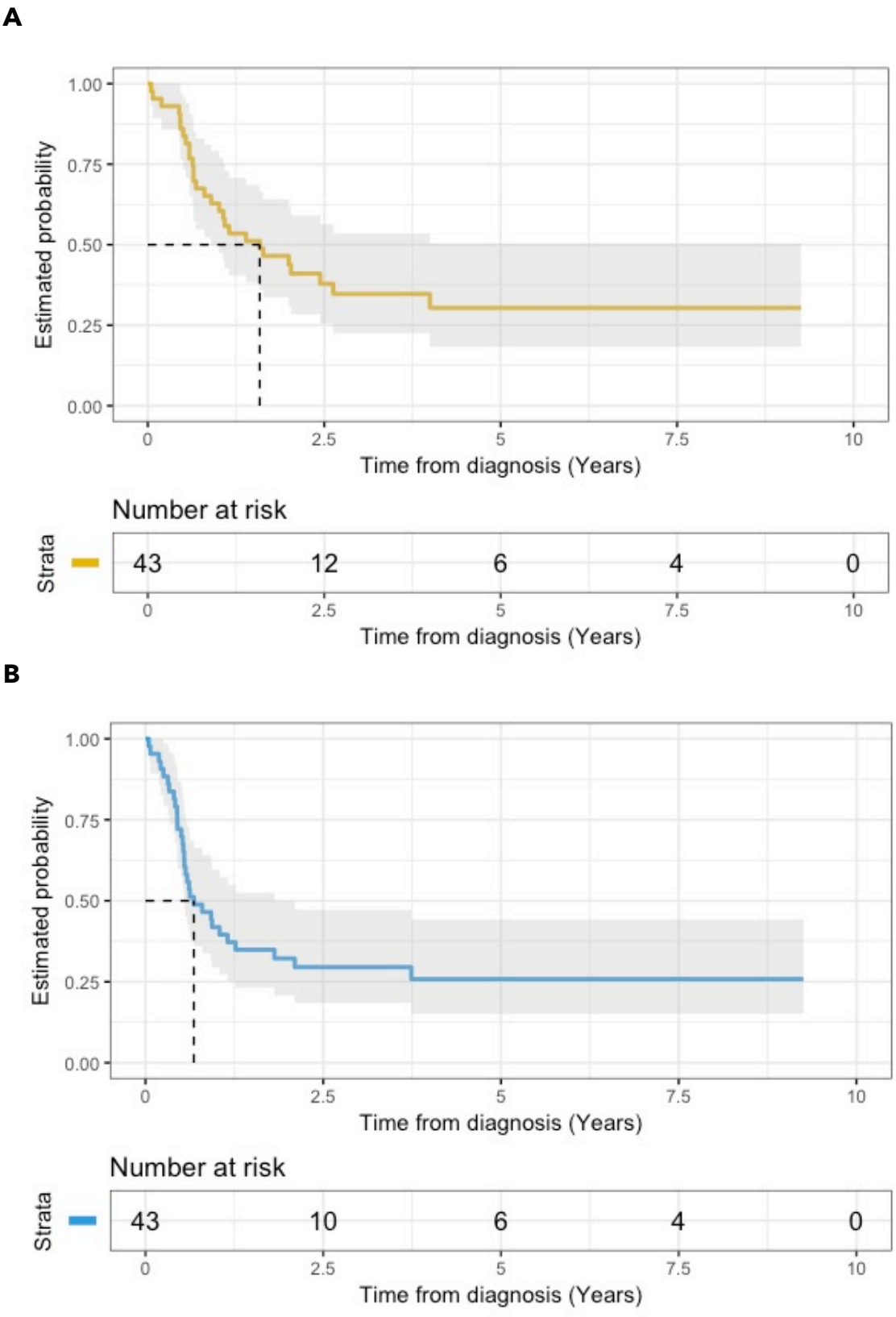


FIGURE 3 Kaplan-Meier Curves for all series.

A, Overall Survival. B, Progression Free Survival

Variable	3-year PFS (95% CI)	Log-Rank	3-year OS (95% CI)	Log-Rank
Gender: Female vs Male	25% (3-48%) vs 36 % (16-57%)	*p*=0.15	23% (1-45%) vs 40% (19-61%)	*p*=0.054
Duration of symptoms (<2 weeks vs >2 weeks)	25% (0-50%) vs 34% (15-52%)	*p*=0.38	15% (0-40) vs 38% (18-57%)	*p*=0.51
Age at diagnosis (<3 years vs >3 years)	11% (0-30%) vs 42% (23-61%)	***p*=0.021**	10% (0-27%) vs 45% (25-65%)	***p*=0.021**
Tumor primary site (Supratentorial vs Other sites)	39% (19-59%) vs 21% (0-43%)	*p*=0.13	37% (17-57%) vs 21 (0-43)	*p*=0.1
Disease extension (M0 vs M1-4)	37% (19-55%) vs 18% (0-41%)	*p*=0.14	38% (19%-57%) vs 18 (0-41%)	*p*=0.03
Histology (PNETs vs Other histologies)	29% (12-45%) vs 42% (24-76%)	*p*=0.4	31% (14-49%) vs 39% (4-73%)	*p*=0.5
Extent of resection (GTR vs Non-GTR)	42% (21-62) vs 18% (0-37%)	***p*=0.03**	41% (19-62%) vs 24% (3-44%)	***p*=0.04**
Radiotherapy (Yes vs No) *	57% (34-80%) vs 7% (0-20)	***p*=0.00**	57% (33-80%) vs 11% (0-26%)	***p*=0.001**

GTR: Gross Total Resection; OS: Overall Survival; PFS: Progression-Free Survival; PNET: Primitive Neuroectodermal Tumors.

In bold letters, those comparisons that reach statistical significance ($p<0.05$)

* The distinction between patients depending on whether they received radiotherapy as frontline treatment (yes vs no) is equivalent to the distinction between patients treated with radiation-inclusive protocols vs patients treated with radiation-sparing protocols, respectively.

TABLE 2 Three-year Progression-Free Survival and Overall Survival according to different baseline variables

4. DISCUSSION

Despite general improvement in the outcome of children with CNS tumors over the last decades, unacceptable mortality rates in patients with the formerly called PNET persist [71, 74, 76, 108, 109].

In addition to their low incidence and biological aggressiveness, these tumors have remained in the shadow of medulloblastoma. Instead of displaying specific approaches, PNET/PB have been historically included in medulloblastoma clinical trials [28, 34, 71, 98, 110, 111].

Moreover, lack of biological understanding of PNET adds to the critical deficiency in specific and novel treatment strategies. Recent molecular genetic studies [62] are extending our knowledge on these tumors, but we are still far from being able to translate this learning into the clinic. Furthermore, these studies suggest that a large proportion of PNET (up to 61% according to Sturm et al.) are being misdiagnosed under conventional histopathological criteria and are, in fact, high grade gliomas, ependymomas, or other tumors. This seems to be in agreement with the preliminary results of the DNA methylation profile of the available samples in our study, with 55% being reclassified to entities different than PNET.

We conducted this study to establish how children with non-medulloblastoma embryonal CNS tumors (so called supratentorial PNET and pineoblastoma) have been managed over the last decade in Spain and identify areas of improvement.

Survival data in our study show a 3-year OS of 35.1% (95%CI 20-50%); in children <3 years this drops to 10% (95%CI 0-27%), whereas in children >3 years it is 45% (95%CI 25-65%). These results are close to a similar population-based study performed on UK (National Registry of Childhood Tumours –

NRCT-) [9], where the authors described a 5-year OS of 32.5% for PNET. Our results are close as well to a similar study conducted by the Canadian Pediatric Brain Tumor Consortium [75], with a 4-year survival of 37.7%. However, they are far from US survival data (NCI's Surveillance, Epidemiology, and End Results –SEER-) reflected on the same study, with a 5-year OS of 57.4%, which was conducted an earlier decade than ours (1996-2005). Of note, our study represents the practice of eight large institutions in our country, all having a pediatric oncologist participating into the CNS tumor group of the national Society. According to the national tumor registry (RETI), there are approximately five to six new cases of CNS-PNET per year in Spain. Our study, spanning 10 years, would have provided data for more than 75% of all cases over that period, but might not reflect the overall nation-wide situation where more than 40 pediatric oncology units treat children and adolescents with cancer [88]. The lack of a central pathology review is another limitation of the study; nevertheless, we put the accent on reporting the current situation with real-world data about clinical outcomes without further delays.

When compared to results obtained from clinical trials, the gap to our real-world data is widened. For instance, young children enrolled on the original Head Start I and II trials (the most frequently applied treatment strategy in our study) had 5-year EFS and OS of 39% (95%CI 24-53%) and 49% (95%CI 33-62%), respectively [73].

This recurrent gap between clinical trials and real-world survival reflects the need for collaboration through international multi-centric trials. Part of this difference can be explained by the strict patient selection of trials. However, it has been repeatedly pointed out in the literature that the recruitment into clinical trials improves the outcomes when compared to unselected populations treated at the discretion of the clinician [4, 9, 29]. Since none of the 43 patients included in this study were recruited into a clinical trial (neither

on first line treatment nor at relapse), this is certainly a point that could be improved. Beyond that, with 17 different first-line strategies, the first step towards improvement should be, in our opinion, to establish a common national strategy for the treatment of these patients.

In the absence of internationally accepted quality standards for treatment of children with CNS tumors, the search for specific aspects to be improved is challenging. This report suggests the importance of several factors: Firstly, attention should be paid to time from initial symptoms to diagnosis. In our study, the median of this interval was two weeks (range 0-12), a good result when compared to data reported for CNS tumors in other countries (Germany 24 days, Switzerland 60 days, UK 100 days) [9, 114, 115]. While different studies have not demonstrated a prognostic impact of time to diagnosis, it remains important to ensure rapid initial diagnosis [116–119].
Also, our report shows that 74% of patients receive surgery within less than a week. However, of the 19 patients with irradiation planned upfront, only 42% received radiotherapy within 49 days of first surgery.

Secondly, extent of resection is a well-known prognostic factor, also reflected in our study, where the experience of the neurosurgical team is key. In our study only half of the patients (23/43) achieved GTR. In this sense, national initiatives such as the creation of reference centers for complex neurosurgery [120] are positive and its impact will be evaluated in the future.

Thirdly, radiotherapy is another crucial factor impacting patients' outcome, but its association with long-term morbidity, particularly in young children, is the major limitation. Hence, postsurgical radiotherapy deferral is common practice in children younger than 3 years, but it remains controversial in older children, especially in the "grey zone" 3-4 years, leading to disparity of criteria among scientific groups and institutions [121]. There were four children older than 4 years in our study that did not undergo RT as first-line treatment.

In one of them this was due to his palliative situation, and he passed away soon after diagnosis. The other three were treated using protocols designed for young children (Head Start II [34] and COG-ACNS0334 -NCT00336024-). All three underwent RT on first relapse, but only one of them was rescued.

Fourthly, there are no established standards to quantify major toxicities, toxic deaths and modifications in chemotherapy time and dose intensity. These treatment protocols have potential significant toxicities and this study will serve as a baseline to measure new indicators prospectively.

The main conclusion of this work is that although we benefit from a well-established health care system in Spain, there is a strong need for collaboration and networking in the treatment of complex CNS tumors such as PNET/PB. The efficacy of the primary care system is reflected in our study in the fast diagnosis of these patients. Survival rates of children with PNET/PB are far from the rates obtained in international clinical trials and a common therapeutic strategy is lacking. This study has served to identify specific aspects to improve in the care of patients with CNS-PNET, namely developing a common treatment strategy, ideally within international collaborative clinical trials, improving referral pathways and reference centers for treatment of complex and rare tumors, maximizing collaboration among pediatric oncology centers, and incorporating new biological markers and the new classification of embryonal CNS tumors. As a result of this study, a subsequent retrospective molecular analysis of archival tumor samples available for this patient cohort has been started in collaboration with European reference centers. Hopefully this will lead to improved outcomes for children with CNS-PNET in the near future.

V. RESEARCH PROJECT #3:

Past, present and future of radiotherapy quality assurance in pediatric CNS tumors:

A European perspective

1. INTRODUCTION

The improved survival rates of pediatric patients with CNS tumors over the last decades lead to a growing concern about long-term sequelae and the quality of life of the survivors [122]. Radiotherapy (RT) continues to be a cornerstone in the treatment of pediatric brain tumors, including embryonal tumors (e.g. medulloblastoma and the previously called primitive neuroectodermal tumors –PNETs) [71, 76, 98, 109]. However, the potential long-term sequelae of CNS irradiation are well known, such as neurocognitive deficits, growth impairment and endocrine toxicities [30–33, 123].

Therefore, minimizing the adverse events and the collateral damage of radiotherapy to the surrounding healthy brain tissue is one of the big challenges of modern radio-oncology [124]. New and more advanced RT techniques and equipment (intensity modulated radiation therapy -IMRT-, particle therapy, gamma knife, etc.) have improved the outcome of children with brain tumors by tackling this issue, at the price of growing complexity and the need for highly specialized centers [111, 121].

These advanced techniques are the result of combining CNS tumor imaging with technology to plan and deliver radiation, the so called conformal RT. Through conformal RT, the radiation dose is targeted to the tumor, minimizing the dose to normal brain structures and hence reducing long-term side effects [125]. Some examples of conformal RT used for the treatment of pediatric CNS tumors are three-dimensional conformal RT, stereotactic RT, IMRT and proton beam RT, also named particle therapy. Regarding the latter, particle therapy (PT) is a growing radiation modality due to the characteristic dose distribution of the proton beam (Bragg Peak phenomenon), which is able to concentrate high doses to the tumor volume while delivering near-zero doses to non-target organs, i.e. sparing normal tissue [126].

In this highly complex technical setting, quality assurance (QA) programs and quality control are essential, considering that deviations in RT can result in increased morbidity and mortality. An example of this is provided by a study of the French Society of Pediatric Oncology (SFOP), in which the RT records of 174 pediatric patients with medulloblastoma were reviewed [127]. The number of major deviations in RT treatment was found to be strongly correlated with the risk of tumor relapse. The authors concluded that the quality of medulloblastoma RT technique is strongly correlated with outcome, and that pretreatment central QA review or standardized computer-designed blocks would improve survival to an extent equivalent to that attributed to adjuvant chemotherapy.

However, the implementation of radiotherapy quality assurance (RTQA) systems is not yet universally achieved. Moreover, scanning the current practices of radio-oncologists and the existing RT resources at a supra-national level constitutes a major challenge. Lievens et al. recently achieved to draw an accurate picture of these practices and resources in Adult Oncology, but not without difficulty and in the frame of a long-term international cooperative project (HERO) [128, 129]. A similar pediatric-specific project is currently being carried out by Demoor-Goldschmidt et al. in the frame of a SIOPe European study, with the first results highlighting the difficulties to obtain accurate and complete data [92].

In order to analyze the situation of RTQA in the treatment of CNS tumors in Europe, this chapter comprises three pieces of work: 1) Literature review of RTQA in pediatric CNS tumors; 2) Review of RTQA aspects in past and current European collaborative trials; and 3) An international survey for radiation oncologists and pediatric oncologists about RTQA practices in Europe conducted in 21 European countries.

2. PAST AND PRESENT

2.1. Current status of RTQA in pediatric CNS tumors in Europe

Some important steps have already been taken regarding the definition of the minimal standards of care for pediatric cancer patients. The best example is the SIOPe (European Society of Pediatric Oncology) guideline, a consensus document describing the minimum quality requirements for a pediatric oncology facility [83].

However, in the field of pediatric radiation oncology, there seems to be a lack of international QA guidelines when it comes to specific treatment modalities for a given pediatric tumor. While some RTQA programs are in place, they are so far implemented in a limited number of European countries and mostly limited to clinical trials. For instance, in Italy a centralized retrospective review system was recently created with the purpose of preparing for the upcoming clinical trials with RTQA demands (e.g. SIOP-PNET5, NCT02066220). This interesting initiative is sponsored by a parent's charity and uses the VODCA software (MSS, Switzerland) to review and assess protocol compliance of patient plans prior to irradiation [130].

Another finding of our review is that there seems to be a paradigm shift from retrospective to prospective RTQA over the last years. While in older studies retrospective quality assessments were the norm [127, 131–133], the most recent and relevant trials for pediatric brain tumors mostly include prospective RTQA programs (Table 1). The case of the SFOP medulloblastoma trials is noteworthy: A prospective RTQA review for craniospinal irradiation (CSI) was introduced in the M-SFOP 98 trial as a result of the conclusions drawn by the retrospective RTQA review of the previous M-SFOP 93 and SFOP.TC 94

trials (for standard and high-risk medulloblastoma, respectively) performed by Carrie et al. (already mentioned above) [127, 134]. The authors recommended the implementation of a prospective, real-time RTQA system following their findings that RT deviations have a negative impact on the outcome, with increased risk of tumor relapse. The subsequent central pretreatment RT review performed in the M-SFOP 98 trial was considered "not only feasible but useful" by the authors of the main publication, noticing a decrease in the number of relapses compared with the previous trial [134].

A further example of this paradigm shift in RTQA is given by the HIT-SIOP PNET trials. In HIT-SIOP PNET 3, the RTQA review was performed retrospectively and published one year later than the trial's primary publication [132, 135]. In HIT-SIOP PNET 4 however, RTQA was performed prospectively by some national groups, and retrospectively within a year for all patients [98]. Additionally, RTQA was considered mandatory to participate in the trial for CSI (optional for posterior fossa/tumor bed irradiation). In the ongoing HIT-SIOP PNET 5 trial (NCT02066220), RTQA is performed prospectively and is mandatory for CSI and all relapses. Furthermore, a QA exercise was performed before the opening of HIT-SIOP PNET 4, in which ambiguities in the draft protocol and areas of inter-clinician variation were found. Consequently, the protocol was revised and improved before the opening of the trial [136].

Clinical trial	Study Start	Study End	Tumor type	RTQA	Level of control	Type of control	Compliance	Publication of RTQA aspects	Main conclusion of RTQA publication
COMPLETED TRIALS									
HIT-SIOP PNET 3 [132, 135]	March 1992	Jan. 2000	MB (M0-M1)	Yes	Global (international)	Retrospective	UNK	Separately from the primary publication (1 year later)	RT duration (<50 days) impacts on EFS
HIT-SIOP PNET 4 [98, 136]	Jan. 2001	Dec. 2006	MB (SR)	Yes	National	Prospective for some national groups; Retrospective (within 1 year) for all patients	Mandatory for CSI; Optional for posterior fossa/tumor bed	QA exercise PRIOR to study opening	Ambiguities in the draft protocol and areas of inter-clinician variation. Consequently, the protocol was revised and improved
HART Milan [28]	1998	2007	MB (MTX)	Yes	Local (only one institution administering RT)	Retrospective	NA	Within primary publication (not detailed)	"RT at the same institution following the local technical guidelines and quality control process"
French M-SFOP 98 [134]	Dec. 1998	Oct. 2001	MB (SR)	Yes	Global	Prospective for CSI, Retrospective for tumor bed boost	Mandatory	Within primary publication (somewhat detailed) and following pre-existing national guidelines	"Central pretreatment RT review is not only feasible but also useful" (no isolated frontal relapse occurred compared

									with seven in the previous report)
SFOP HR [137]	Jan. 1993	June 1999	MB (HR)	Yes	Global	Retrospective	Mandatory	Within primary publication (somewhat detailed) and following pre-existing national guidelines	EFS not statistically different for patients with no or one major deviation or for patients with more than one, possibly due to the low number of patients, but also because the impact of a deviation might be less when the dose is higher
LGG 2004 [138]	April 2004	April 2012	LGG	No *	National	Retrospective	Mandatory (not clearly specified)	No mention in primary publication	NA
HERBY [139]	Oct. 2011	Feb. 2015	HGG	UNK	UNK	UNK	UNK	No mention in primary publication	NA
ONGOING TRIALS									
HIT-SIOP PNET 5 (NCT02066220)	June 2014	Open	MB (SR)	Yes	National	Prospective	Mandatory for CSI and any relapse; Optional for posterior fossa/tumor bed	NA	NA

SIOP-EP-II (NCT02265770)	April 2015	Open	EP	Yes	National	Retrospective (within 4 months)	Mandatory (although not clearly specified)	NA	NA
SIOP CNS GCT II (NCT01424839)	Oct. 2011	Open	IGCT	No *	National	Retrospective	Mandatory (not clearly specified)	NA	NA

CSI: Craniospinal Irradiation; EFS: Event-Free Survival; EP: Ependymoma; HR: High Risk; IGCT: Intracranial Germ Cell Tumor; LGG: Low Grade Glioma; MB: Medulloblastoma; MTX: Metastatic disease; NA: Not Applicable; RT: Radiotherapy; RTQA: Radiotherapy Quality Assurance; SR: Standard Risk; UNK: Unknown.

* Only data collection

Of note: Treatment strategies for infants are not included (as they do not include RT).

TABLE 1 RTQA aspects in recent clinical trial protocols for pediatric CNS tumors

These examples of RTQA, although effective in the clinical trials setting, leave patients treated outside that context behind. This may widen the already existing gap between the outcome results obtained from clinical trials and the results obtained in real-world settings [9]. An example of this gap is given in the study by Vivekanandan et al., in which they reported the UK experience of using the HART-Milan strategy for the treatment of metastatic medulloblastoma [29]. In the real-world setting of 14 hospitals in the UK, the obtained results were far from those obtained in the original mono-centric trial (56% vs 77% 3-year OS). Furthermore, the confidence interval in the UK study (95%CI: 38%-71%) included the historical result of 40%. Therefore, the authors concluded that the reason they could not replicate the original trial results may be due to several factors: 1) statistical chance (expressed as the wide 95%CI for both series), 2) differences in patient characteristics, case selection, treatment delivery, and 3) the nation-wide implementation of a regimen previously tested in a single center. Additionally, a different group exploring neurotoxicity associated with this regimen in a separate UK cohort of patients discovered cases of severe and disabling neurotoxicity, which were not observed in the original trial [140]. The severe reported cases of myelitis and of other grade 3-4 CNS toxicities seemed to associate with the overlapping of upper cervical spine within posterior fossa boost volumes in conjunction with neurotoxicity associated with thiotepa [141, 142]. As a result of both real-world studies, the HART-Milan strategy was discontinued since 2014 in the UK, due to lower than expected survival rates and the concerns regarding neurotoxicity [29, 140].

2.2. Survey: Current practices of radiation oncologists across Europe

We have performed a survey about the current practices of RTQA in pediatric brain tumors across Europe with an "ask-the-expert" approach. The aim is to have a general perspective of the current situation and of the level of awareness of healthcare professionals on the available infrastructures and programs. We hereby present the results.

2.2.1. Methodology

One pediatric radiation oncologist and one pediatric oncologist of each European country (29 countries included: 23/27 official EU members, plus Israel, Norway, Serbia, Switzerland, Turkey and the UK) specialized in the treatment of CNS tumors were contacted in February 2018 by email and invited to complete an online 12-item questionnaire (Appendix 1).

To compare the number of RT centers between countries, the total number was divided by the population of each country. Population data were obtained from the Central Bureau of Statistics for Israel and from Eurostat for the rest of the countries [143, 144].

2.2.2. Results

Out of the 29 contacted countries, 21 (72%) responded and participated in the survey (Figure 1). A total of 48 experts were contacted: 18 (90%) out of 20 contacted radio-oncologists responded to the survey; 15 (54%) of 28 pediatric oncologists responded (Figure 2).

FIGURE 1 Participation across countries

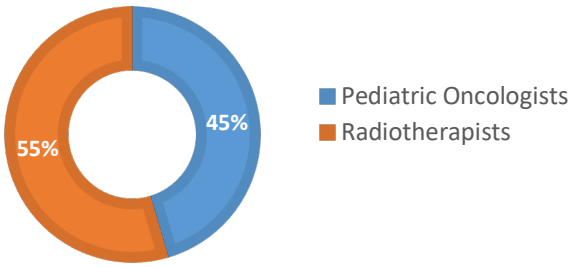


FIGURE 2 Type of respondents

The number of public RT centers that treat pediatric patients with CNS tumors varies across countries, with a median of 3.7 (range 0.6-10.7) per 10 million population (Figure 3).

Most participants (67%, 22/33) agreed or strongly agreed that there is a known and well-established referral network for the RT treatment of pediatric patients in their respective countries. However, some showed concern that this network is "not official", or still under construction, or only useful for patients treated within clinical trials (Figure 4).

While only 19% (4/21) of the countries have a national pediatric radiotherapy society, 64% (21/33) of the participants responded that the level of involvement of pediatric radiation oncologists in the meetings and activities of the respective national pediatric oncology societies is "somewhat sufficient" or "sufficient". The rest of the participants responded that the involvement is "somewhat insufficient" or "insufficient" in 30% (10/33) of the cases, and "Neither insufficient nor sufficient" in 6% (2/33) (Figures 5 and 6).

Only 48% (10/21) countries have national consensus guidelines for the treatment of pediatric CNS tumors (Figure 7). National RTQA programs are in place in 33% (7/21) of the participating European countries (Figure 8). These programs are very heterogeneous: in Ireland, the participant responded that "all radical cases undergo prospective peer review performed by adult radiation oncologists"; in Belgium, the RTQA program works only for the clinical trials SIOP-PNET 5 and SIOP-EP-II so far; in Denmark, every RT dose plan is reviewed in a biweekly meeting with Swedish pediatric radiation oncologists; in France, the Aquilab® system is used for all prospective trials; in Germany, the HIT network is in place for all pediatric CNS tumor studies; in the UK, there is a national RTQA team for all trials as well; and in the Slovak

Republic, there is an RTQA program that reviews the imaging system, planning system, irradiation equipment and plan implementation.

Only three countries (14%; 3/21) have a central storage system for RT data in place (Figure 9). In all of them (Denmark, France and Germany), the complete DICOM radiotherapy plans are collected as part of the data.

Pediatric patients with CNS tumors have access to a particle therapy facility in almost all (95%; 20/21) participating countries (nationwide or elsewhere, supported by the public health system) (Figure 10). In Turkey, particle therapy can be accessed abroad with the support of the national health system in some particular cases.

Most participants (85%; 28/33) agreed or strongly agreed that all pediatric patients with CNS tumors are granted equal access to radiotherapy in their respective countries (Figure 11). Five respondents showed concerns that this might not be the case all over their respective countries (Israel, Italy, Spain, Switzerland and Turkey). For example, the Italian expert believed that patients from the South of Italy have worse access to well-trained teams. The Spanish expert thought that "most of the patients that need this treatment will get it, but probably the quality of this therapy and the expertise needed to provide it is not equal for all". The Turkish expert believed that the geographical distribution of advanced pediatric radiotherapy centers is not well balanced: "Centers in the large cities of western and central Turkey capable of delivering high-quality radiotherapy, whereas conditions are not satisfactory in eastern parts of Turkey".

Almost all (91%; 30/33) consulted experts believe that the patients would benefit to a considerable or to a great degree from a European RTQA guideline for pediatric brain tumors (Figure 12 and Table 2).

The most relevant results of the survey are presented in the following figures and table (Figures 3-12; Table 2).

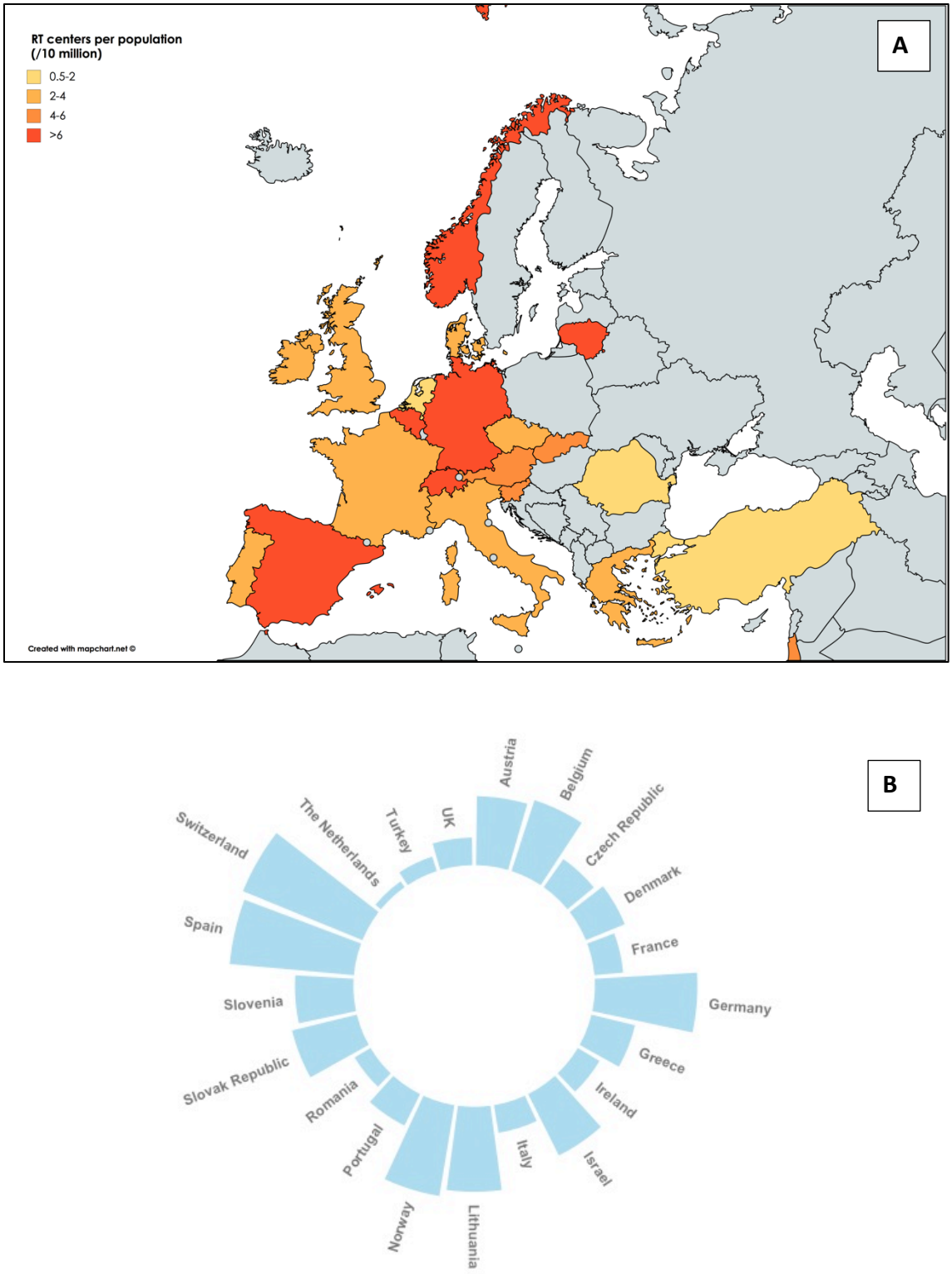
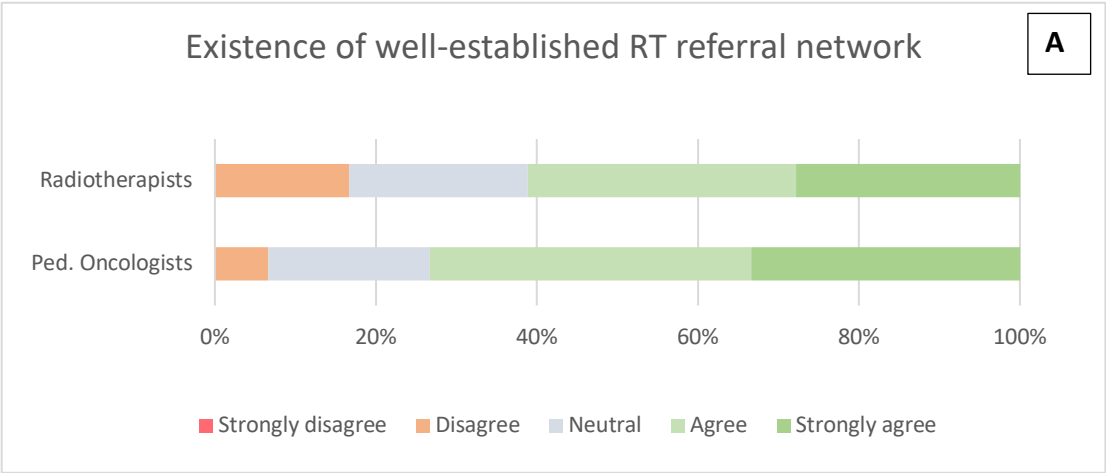


FIGURE 3 RTQA centers for pediatric CNS tumors per country population. A, Number per 10 million population. B, Comparison between countries.



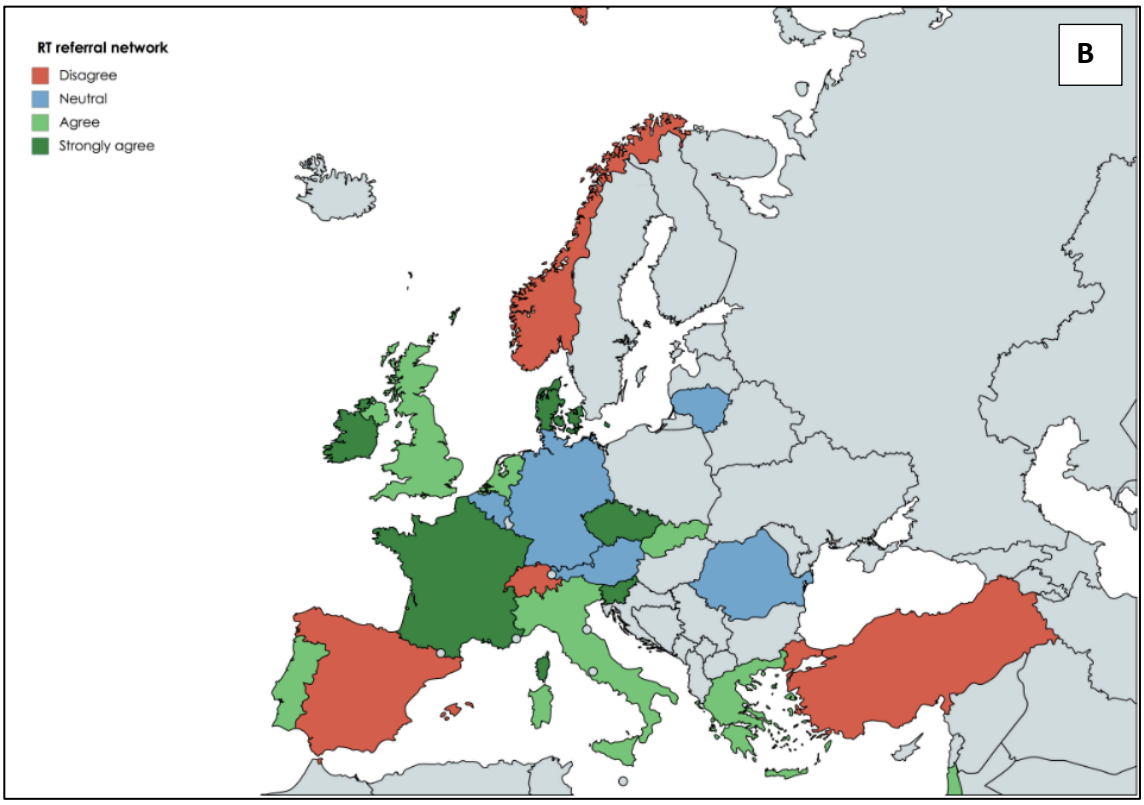


FIGURE 4 Existence of a well-established national referral network for the radiotherapy treatment of pediatric patients. A, Opinion among all participants. B, Map showing responses by country. Of note: In case of disagreement, the opinion of the radiation oncologist is highlighted in the map.

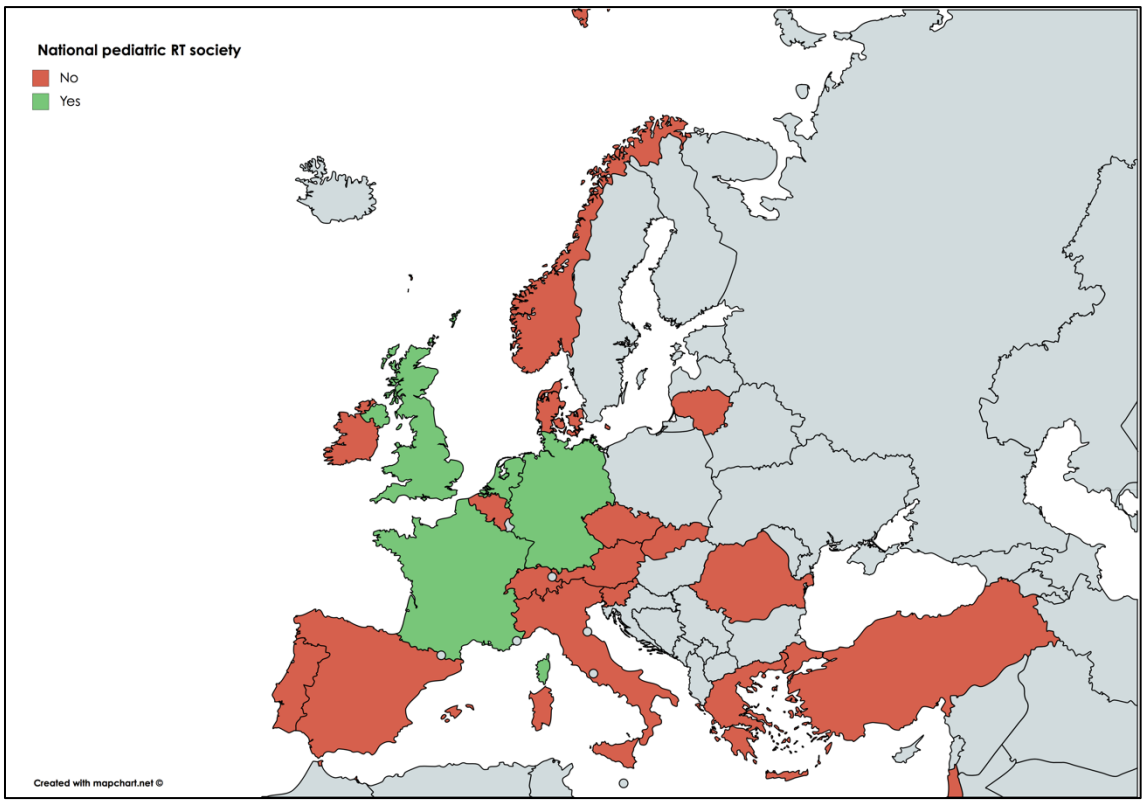


FIGURE 5 Existence of a national pediatric radiotherapy society

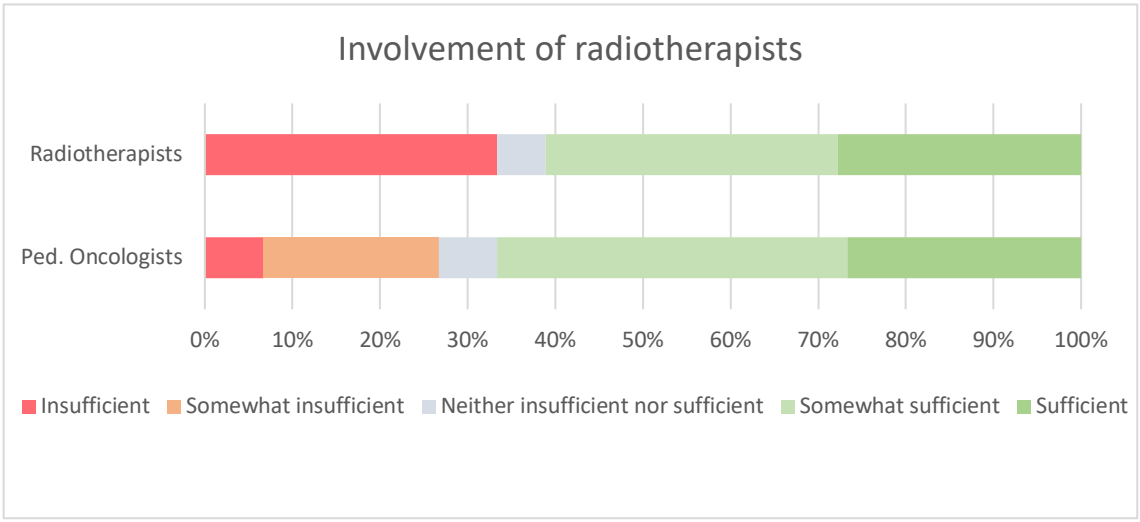


FIGURE 6 Opinion about the level of involvement of pediatric radiation oncologists in the meetings and activities of their national pediatric oncology societies.

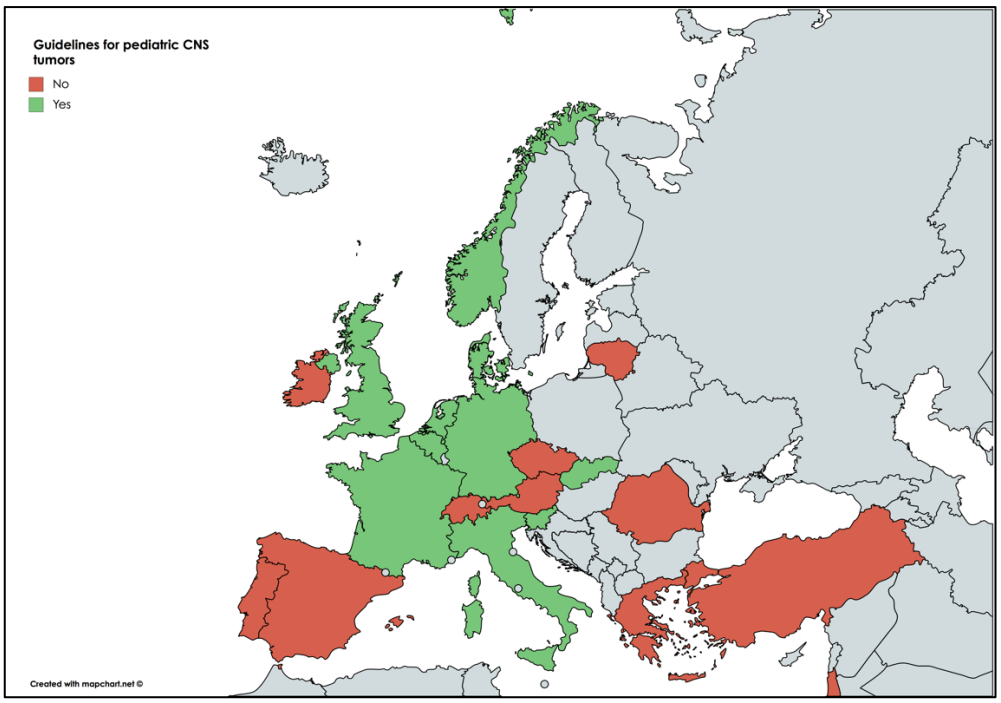


FIGURE 7 National guidelines for the treatment of pediatric CNS tumors.

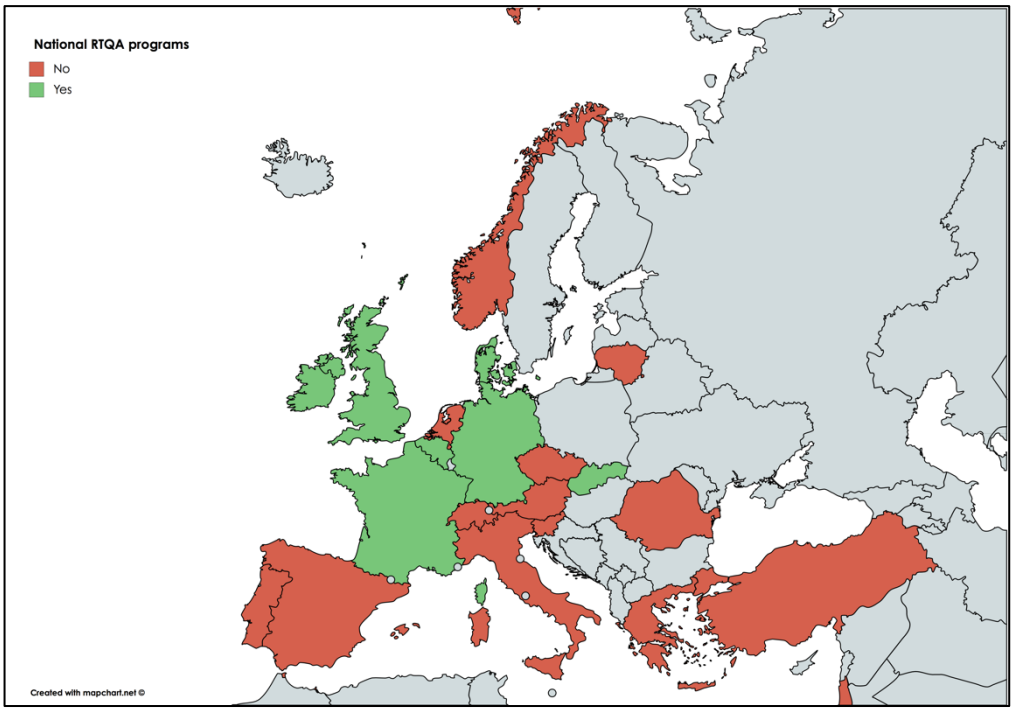


FIGURE 8 National radiotherapy quality assurance programs for the treatment of pediatric brain tumors

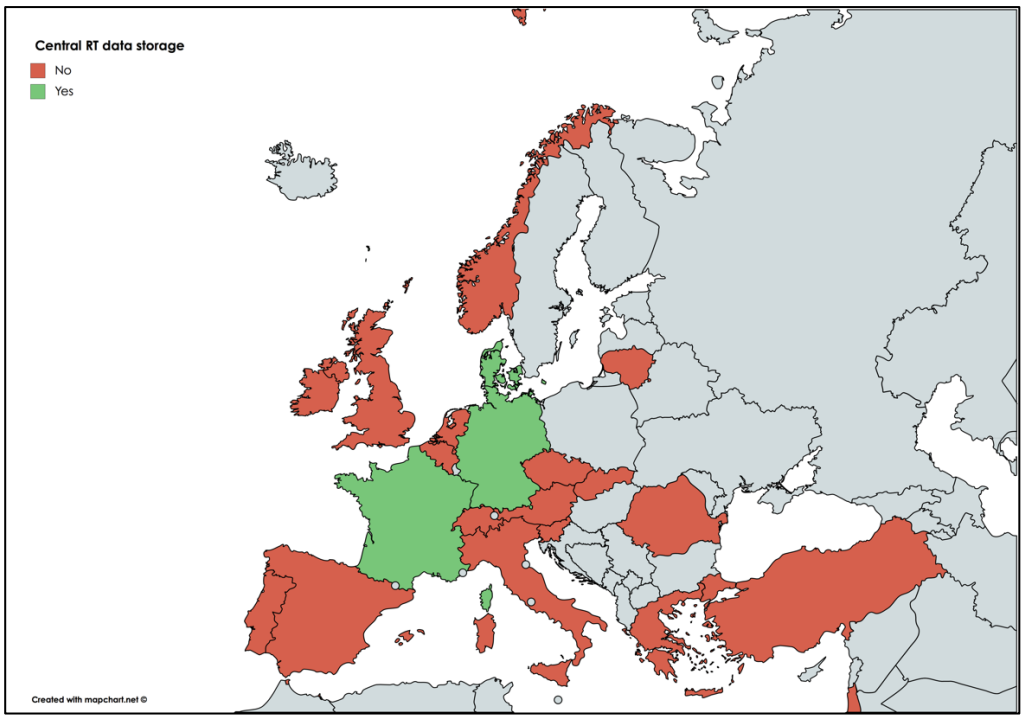


FIGURE 9 Central storage systems for radiotherapy data

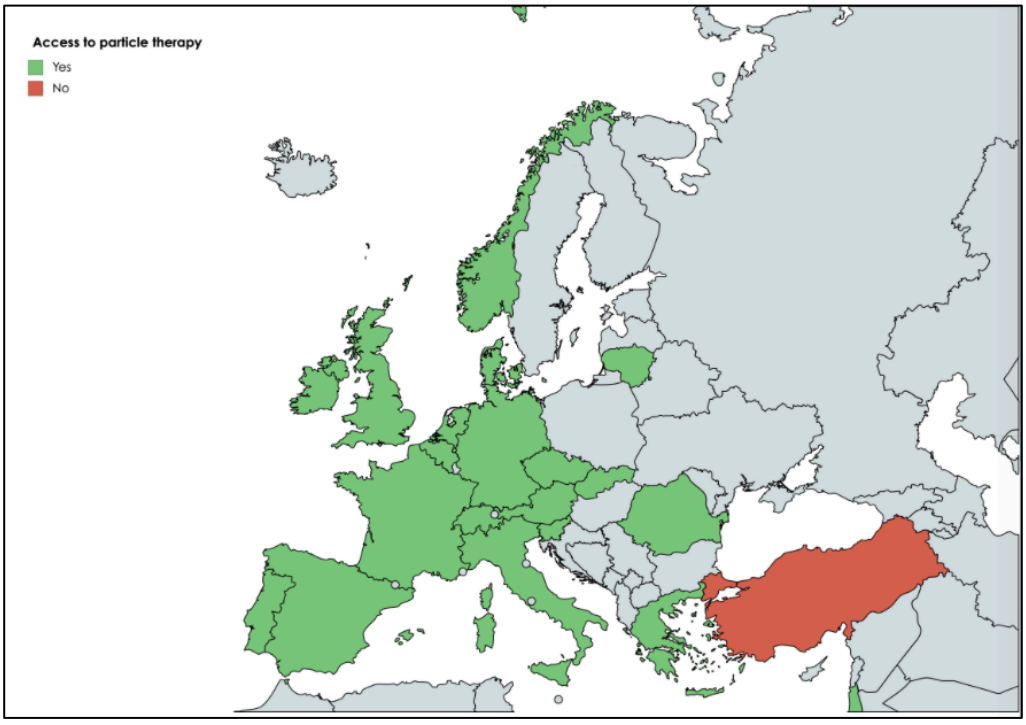


FIGURE 10 Access to a particle therapy facility (nationwide or elsewhere, supported by the public health system)

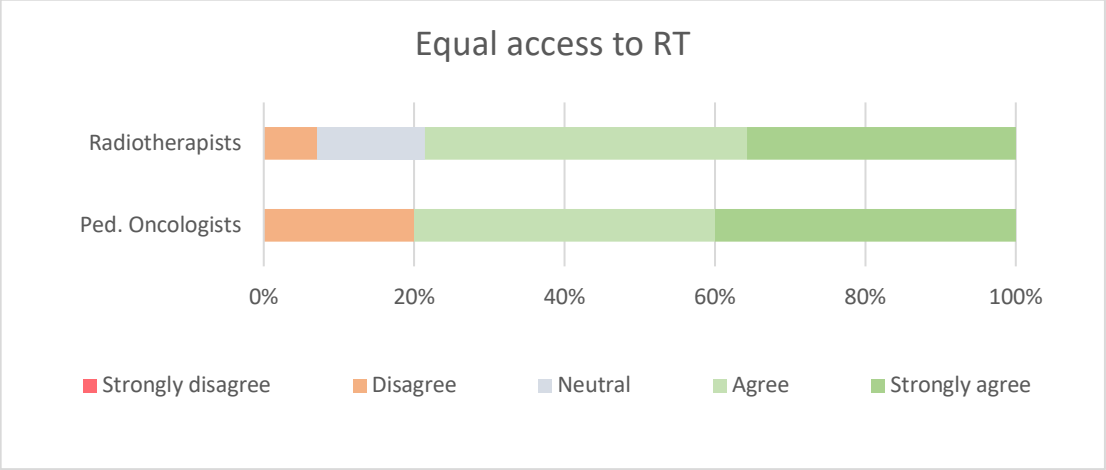


FIGURE 11 Existence of equal access to radiotherapy across all pediatric patients with CNS tumors at a national level according to the participating experts

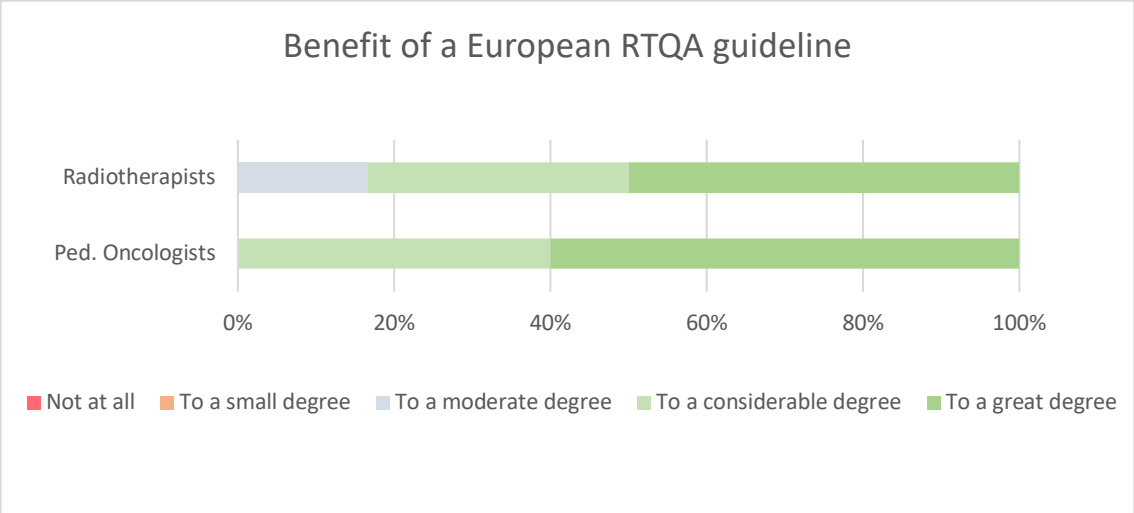


FIGURE 12 Potential benefit for the patients of a European RTQA guideline for pediatric CNS tumors according to the participating experts

Comments about the possible benefit of a European RTQA guideline
"Unifying radiotherapy will ascertain high standards in Europe and may help less experienced centers. It will furthermore facilitate comparisons between different treatment studies."
"I think it would be great to define a kind of standard treatment that is good clinical practice for all children. The problem will be economically, the balance between evidence based good clinical practice and what is achievable/affordable in the individual countries."
"There is a strong international wish to harmonize structures, which is ongoing based on the QUARTET platform. Harmonized guidelines would to my understanding be helpful as a basis for definition of goals, measures and necessary resources."
"We are completely in favor of an European Network for Quality control in Radiotherapy, as well as in other issues, namely imaging, pathology and biology... Only with this kind of procedures we could treat patients with the state of the art. This is a particularly important issue for small countries."
"It would be really useful to standardize protocols across the EU, as we recruit into the same trials, and would all be working from the same baseline then."
"We would be very happy to have such guidelines and some kind of supervision as well, especially for some difficult cases. This is true, in my opinion, for all small countries, as ours."
"I think that this should stay guidelines and not obligations. Patients would mainly benefit from better collaboration between the pediatric radiotherapists and between the pediatric radiotherapists and the pediatric oncologists on a national level."
"It would be a good initiative, however resources are scarce for this extra workload."
"Based on the QA experiences within PNET 5 a great benefit of QUARTET can be expected."
"Yes this would be something very helpful. It is something that is being tried to be developed for some tumors (ependymoma) but not polished yet."

TABLE 2 Top 10 comments of the participating experts about the potential benefit for the patients of a European RTQA guideline for pediatric CNS tumors

3. FUTURE

3.1. First steps and future development

To address the above described challenges, first steps are being taken at different levels. At a national level, there are two prominent examples of good initiatives in European countries: in the Netherlands and in Belgium. In the Netherlands, there is a novel program for proton-therapy, "ProTraIT", which is comprised within the Dutch Translational Research IT project (TraIT). This is a nationwide IT infrastructure for data and workflow management targeted at the needs of translational projects [145]. It is within the frame of this wider platform that ProTraIT has been developed to centralize the data of all patients receiving proton-therapy (children and adults) and to perform model-based approach studies enabling individual double-planning, in which the best hypothesized outcome is chosen.

While according to our survey only 29% (6/21) countries have an established national central storage system for RT data, this is already changing. A recent initiative in Belgium aims to implement a central record of the radiotherapy planning of every pediatric patient, in the frame of the Belgian Cancer Registry [146]. This long-term storage will eventually allow for a retrospective control of frontline treatments while no prospective check is foreseen. This is especially useful in the relapse setting, as it can improve the quality of the salvage radiotherapy; moreover, ensuring RT data are available at a very late stage is crucial to properly build multivariate toxicity models addressing long term Normal Tissue Complication Probability (NTCP). Accurate NTCP models are essential to create international treatment guidelines for optimal sparing of organs at risk. Both the Dutch and the Belgian initiatives are excellent examples of how existing research infrastructures can

be used for a downstream purpose, in this case RTQA for pediatric brain tumors.

At a wider, European level, another major step is seen in the recently created European platform "QUARTET" ("QUAlity and excellence in RadioTherapy and imaging for children and adolescents with cancer across Europe in clinical Trials"), which aims to build a radiotherapy QA platform across all pediatric malignancies in Europe in trials [100]. It is constituted in partnership between SIOPe and the European Organisation for Research and Treatment of Cancer (EORTC). QUARTET will help implement RTQA programs in several SIOPe trials including SIOP-PNET 5 (NCT02066220) and SIOP-EP-II (NCT02265770). Although, in its current state, it only includes patients participating in clinical trials, it will eventually expand to patients treated outside of trials as well.

The weaknesses of our study need to be acknowledged: 1) The performed literature review of RTQA in pediatric CNS tumors is, although extensive, not a systematic review; 2) The review of RTQA aspects in past and current European trials is not exhaustive; however, the purpose was to highlight some relevant examples to expose the ongoing paradigm shift towards prospective RTQA in clinical trials; and 3) Not all European countries responded to the international survey. Nonetheless, the inclusion of 21 participating countries from all European regions (Northern, Western, Eastern and Southern/Mediterranean) allows to draw a rather comprehensive European perspective.

3.2. What is the dream? Identified areas of improvement

The performed review and survey have helped identify the following areas of improvement.

1. Standardization of treatment: Guidelines

Clinical guidelines are a useful tool and an affordable and straightforward approach towards standardization of treatments, especially for the management of highly complex diseases such as pediatric CNS tumors. This is particularly of importance for patients treated outside clinical trials. However, through our survey we found out that only 48% of the participating countries have national consensus guidelines for the treatment of pediatric CNS tumors.

National and/or international guidelines can be a first step to unify strategies, facilitate QA and improve the management of children with CNS tumors. Participation in frontline randomized clinical trials remain the standard treatment in pediatric oncology, but still, guidelines are often needed for aspects not covered in clinical trials or time periods where these are not open.

Moreover, almost all (91%) consulted experts believe that the patients would benefit to a considerable or to a great degree from a European RTQA guideline for pediatric brain tumors. There seems to be an increasing awareness of the necessity for a common effort across European CNS tumor specialists to ensure high-quality RT treatment for these complex patients.

Looking at similar experiences in adult oncology, several international, disease-specific radiotherapy guidelines exist for adult cancers, based on published level 1 or 2 evidence and/or expert consensus, detailing delineation and dose recommendations for the specific disease (e.g. for glioblastoma [147, 148]. While level 1 or 2 evidence is not always available, especially in a

pediatric and rare disease context, consensus is certainly reachable. In parallel to generating consensus guidelines, regular audit procedures should be implemented at a local, national and international level to ensure the centers comply with the directives of the guidelines. This could raise the standards for RT treatment beyond clinical trial protocol provisions.

2. Multidisciplinary work: Collaboration between pediatric oncologists and radiation oncologists

Multidisciplinary team work is essential for the treatment of pediatric CNS tumors. The importance of multidisciplinary tumor boards for pediatric tumors has been already reported [149, 150]; it is essential that radiation oncologists participate in these meetings. More concretely, a close and smooth interaction between pediatric oncologists and radiation oncologists is key to be able to implement new RTQA initiatives. In that regard, it is already a good sign that the answers we obtained from both types of specialists were similar. About two thirds (64%) of the consulted experts believe that the level of involvement of pediatric radiation oncologists in the meetings and activities of the respective national pediatric oncology societies is adequate ("somewhat sufficient" or "sufficient"). While this is a positive fact, it leaves room to improvement.

Moreover, only one fifth (19%) of the participating countries have a national pediatric radiotherapy society. There might not be a need for independent societies, especially in small countries where the number of these specialists is low; but this is yet another reason to call for an increased involvement of radiation oncologists in the pediatric oncology societies and supranational initiatives. Beyond this, European platforms such as QUARTET

should be encouraged and strengthened with the incorporation of new members.

3. Central storage of RT data

As with other QA systems, an important component is the management of data. In that regard, an important step towards the implementation of wide RTQA systems is the central storage of RT data, which is currently done in 29% of the European countries according to our survey. An optimal storage should include the full planning and the final report, with the complete DICOM RT plan and any auxiliary imaging used to define the target(s); furthermore, all treatment deviations should be documented and stored as well. Following the Belgian example, an affordable first approach for this storage could be the use of the national cancer registries. The use of a shared database has the additional advantage of facilitating the link with other relevant clinical and translational data (long-term follow-up, biobanking, pathology reports, tumor genomics, etc.) while maintaining compliance with the new European Data Protection Regulation [151].

While national registries and other initiatives such as the Dutch ProTraIT platform are excellent first steps, an international storage would have, without saying, many additional advantages. Additionally, the use of pan-European platforms would allow to include all types of pediatric patients with brain tumors, regardless of their inclusion in clinical trials. This would help to amplify our knowledge with real-world data, and eventually reduce the already mentioned gap between the outcome of patients enrolled in clinical trials versus the outcome of those treated outside that frame.

4. RTQA programs

RTQA is an essential part of the treatment of pediatric brain tumors and, as such, it should be further developed, particularly at reference institutions. According to our survey, only one third (33%) of European countries have RTQA programs in place for the treatment of pediatric brain tumors; this is certainly a point to be improved across Europe. Additionally, the existing programs are heterogeneous, with different levels of complexity.

A good start for the construction of RTQA programs is to implement systematic review systems of both, frontline and relapse RT plans. The ultimate aim is to have a prospective RTQA system in which each new RT plan is reviewed by an international expert panel before the treatment is applied to the patient, which is challenging due to time constraints in clinical practice. This is especially the case in children with brain tumors, in which the clinical situation may not allow delays in the start of the treatment, or in which it is already well proven that a late onset of RT reduces survival, such as the case of medulloblastoma [93]. This more ambitious approach of a prospective review is being currently implemented in some trials (e.g. SIOP-PNET 5, as already explained). However, until this can be extended across all types of CNS tumors and to patients treated outside clinical trials, the standards could be improved by a systematic continuous retrospective review.

5. Equal access to RT for pediatric patients with CNS tumors across Europe

At a national level, no differences were reported in the access to RT treatment for children and adolescents with CNS tumors. The majority of experts participating in the survey (85%) agreed that this was the case in their respective countries. Additionally, two thirds (67%) believed that there was a

well-established national referral network for the RT treatment of pediatric patients.

As shown by several works in the literature, at a European level, inequality prevails [91, 152, 153]. There is a well-known inequality of outcomes for pediatric cancer patients across Europe [91]. One of the reasons could be the imbalance in radiotherapy, with a wide range of levels of access to best-care facilities and specialists across European countries [92]. We have corroborated this with the findings in our survey: there is a wide variability in the number of public RT centers that treat pediatric patients with CNS tumors across countries, with some countries having 20 times more centers per million population than others. While the optimal number of centers is not established (and is probably in neither of both extremes), these data might possibly be another sign of inequality across Europe.

A specific area which deserves attention is particle therapy, with fewer centers and less experience, and where indications, toxicities and long-term follow-up should be standardized. In this case, there is often already a centralized referral pathway, due to the scarcity of available facilities in each country, with almost all European countries (95%) granting access to PT within the public health system, according to the survey. However, this situation might change: According to the Particle Therapy Co-Operative Group (PTCOG), there are currently 75 particle therapy centers in operation, 41 centers under construction and 25 in planning stage all over the world [154]. Future work should include achieving international consensus for the indications of PT, as well as establishing appropriate studies and networks to manage and conduct long-term follow up for these patients.

Existing national and European referral networks for RT for pediatric brain tumors should be expanded and new ones created where none are

currently functioning. This is particularly relevant for complex radiation treatments. The recently launched European Reference Network for Pediatric Oncology (ERN PaedCan) [155] will be an appropriate framework in which to start implementing referral pathways for RT in pediatric brain tumors and promoting RTQA initiatives.

In conclusion, RTQA understood as an ongoing audit of our medical practice, is essential in all aspects of pediatric oncology, but even more so in the highly technical and complex field of RT for CNS tumors. Several positive initiatives, both national and international, are being undertaken to implement RTQA in the treatment of pediatric patients across Europe, and there is still room for improvement. Creating a European RTQA guideline for pediatric CNS tumors, improving the collaboration between pediatric oncologists and radiation oncologists, building a European central storage system for RT data, implementing international RTQA platforms such as QUARTET, and promoting European referral networks to reduce inequality across countries are some of the measures that will hopefully contribute to improve the still dismal outcome of pediatric patients with CNS tumors and reduce long-term toxicities.

VI. DISCUSSION

Major advances in the treatment of pediatric cancers have been made over the last 40 years, turning a predominantly incurable disease into a disease with overall survival rates above 80% [6]. This has been mainly achieved through large international collaborative trials and multidisciplinary treatment. Furthermore, in this rare disease context, the enrollment of patients in frontline randomized clinical trials (RCTs) has become the standard treatment in pediatric oncology.

However, international RCTs are not always accessible, for example for particularly rare tumors (such as CNS-PNETs) or for time periods between the opening of consecutive trials. Therefore, positive results obtained in RCTs should be reproducible in real-world settings, generating a genuine patient benefit across the globe. It is here where observational research plays a major role, be it with large population-based studies or with smaller, real-world patient cohorts, to investigate and corroborate the effects of new therapies or new strategies among patients treated in routine practice. As Booth et al. pointed out [156], observational studies are necessary and complementary to ensure that results of RCTs translate into benefits for the general population, that is, to demonstrate effectiveness. Ording et al. recently described some of the advantages of observational studies [157], namely the ability to investigate real-world safety issues (e.g. previously unrecognized concerns) by examining rare endpoints or multiple endpoints at once; the inclusion of real-world patients from clinical practice, such as frail patients with comorbidity that are usually excluded from clinical trials; and the possibility to examine the effectiveness of interventions applied in clinical practice and of long-term clinical outcomes, which are often not feasible to study in RCTs (Table 1).

Characteristics	Clinical trials	Observational studies
Exposure	- Intervention that may differ from clinical practice - Usually 1/2 interventions	- Standard clinical practice - Any number of exposures
Population	Usually restricted (younger patients, no comorbidity, …)	Can include entire patient populations
Confounding control	Randomization limits confounding	Confounding by indication and unknown confounding is always a concern
Compliance	Measurable	Difficult to measure
Cost	Expensive	Inexpensive (registries)
Time frame	- Time consuming - Too short for rare endpoints	- Often fast (if registries) - Feasible for rare endpoints
Endpoints / Outcome	- Standardized measure of endpoints - Blinding is possible	- Restricted by routine clinical practice - No blinding

TABLE 1 Characteristics of clinical trials versus observational studies. Adapted from Ording et al., 2016 [157]

Additionally, clinical audit is a key element of clinical governance and good medical practice. Regular auditing practice allows to explore whether treatment strategies are being optimally delivered [158, 159].

A major goal of both, observational studies and clinical audits, is to ensure real benefit for patients, i.e. to close the gap between clinical trials and the real-world setting. This was precisely the global aim of this thesis, namely to combine the results of analyzing real-world cohorts of patients with data extracted through clinical audit tools in order to better understand the mentioned gap and to propose ways of reducing it.

A good example of how dramatic the gap can be occurred when the HART-Milan strategy for metastatic medulloblastoma was generalized from a

single institution to a wider international setting, as reported by Vivekanandan et al. [29]. Gandola et al. reported a 77% 3-year OS in a single institutional cohort of patients with metastatic medulloblastoma, a considerable improvement in comparison with historical controls with 3-year OS of 40%. [28]. However, when the treatment strategy was implemented at a national level in the UK, the results obtained were far from the original, with a 3-year OS of 56% (95%CI: 38%-71%). Furthermore, severe cases of neurotoxicity, which were not observed in the original trial, were found in a separate UK cohort [160]. As a result of these real-world, observational studies, the HART-Milan strategy was abandoned in the UK and internationally, which accounts for the importance that these studies can have.

Beyond this general problematic of clinical trials versus real-world settings and in spite of the improvements in the outcome of children and adolescents with CNS tumors over the last decades, mortality and morbidity rates remain unacceptably high. Hence, this group of diseases still constitutes a major challenge in pediatric oncology being one of the leading causes of death due to disease in childhood and a major cause of long-term disability [6, 3].

To tackle this issue, several initiatives are currently being pursued by research groups all over the world, some of them particularly avant-garde and groundbreaking, to name a few: the advances in the knowledge of the tumor biology that have led to the discovery of four well-defined molecular subgroups of medulloblastoma and of new entities among the so called PNET group thanks to the new methods of molecular profiling (e.g. methylation and genomic profiling), which will soon change the way in which CNS tumors are diagnosed and classified [21, 62, 79]; the technological progress within the

classical treatment modalities, e.g. particle therapy, gamma-knife, and novel surgical techniques [124]; and the discovery of new drugs, especially with the uprising of targeted therapies and immunotherapy, which are paving the way towards Precision Medicine [43, 161, 162].

While this is certainly an exciting era, it will take time and resources until all these advances are translated into real, tangible benefit for patients. In the meantime, in this wild race towards the top-notch therapies, we might be forgetting the basics: to optimize what we already have, auditing our current practices and developing tools to ensure the highest quality in the management of our patients are implemented across all pediatric oncology centers in Europe and globally.

The aim of this thesis was to analyze the current multimodal management of children and adolescents with CNS tumors, to identify weak points and propose pragmatic measures that can improve the outcomes of patients at three levels: local, national and international. Three research projects were carried out to reach this objective.

Research Project #1: "Improving the quality of care in the molecular era for children and adolescents with medulloblastoma"

The aim of this study was to present a real-world cohort of children and adolescents with medulloblastoma, to search for weak points in their management that can be improved at a local/institutional level. We performed a monocentric review of all pediatric patients with medulloblastoma treated at Hospital Niño Jesús, Madrid, between 2003 and 2016. While we acknowledge some relevant limitations of the study due to its retrospective and monocentric nature, the derived conclusions are highly pragmatic and can be extrapolated to other institutions, ultimately improving the quality of care of the patients.

The clinical audit revealed several areas of improvement, and we subsequently proposed a set of 27 quality indicators that may be used in the setup of a quality assurance system for the management of pediatric patients with CNS tumors. This implementation of a QA system is our first proposal to improve the outcomes of these patients. Other proposed measures include maximizing the inclusion of patients in international clinical trials, expanding the local Clinical Trials Unit, establishing a central pathology review, accelerating the translation of the new molecular knowledge into daily practice through the use of up-to-date biological markers, and implementing a neurocognitive and QOL evaluation program.

These measures will hopefully improve the outcomes of children and adolescents with medulloblastoma in the near future, starting at a local/institutional level.

Research Project #2: "Management and outcome of children and adolescents with non-medulloblastoma CNS embryonal tumors in Spain: Room for improvement in standards of care" [101]

The two main aims of this study were to present a tumor-specific, national real-world data cohort (as opposed to clinical trials data) of children and adolescents with CNS-PNET/PB and to identify weak points and quality indicators that can be implemented to improve the still dismal outcome of these patients. The major interest in studying a tumor-specific cohort of PNET relies on the fact that, in addition to their low incidence and biological aggressiveness, these tumors have historically remained in the shadow of medulloblastoma, with a lack of specific approaches.

We reviewed all pediatric patients with non-medulloblastoma CNS embryonal tumors treated in the eight major oncology centers in Spain between 2005 and 2014. We found a dismal outcome, especially when compared to patients included in clinical trials. Following our analysis, we proposed establishing a common national strategy, implementing referral circuits and collaboration networks, and incorporating new molecular knowledge into routine clinical practice as accessible measures that can improve the outcome of these patients.

Furthermore, as a direct result of this study, a retrospective molecular analysis of archival tumor samples available for this patient cohort was started in collaboration with European reference centers; this will ultimately result as well in a benefit for children with this rare type of tumor.

Research Project #3: "Past, present and future of radiotherapy quality assurance in pediatric CNS tumors: A European perspective"

The aim of this study was to present an overview of the situation of radiotherapy quality assurance of pediatric patients with brain tumors on an international level, and our perspective on the challenges of the future. To have this general perspective of the current situation, we analyzed past and current clinical trials protocols for pediatric CNS tumors and performed a survey about the practices of RTQA in pediatric CNS tumors across Europe with an "ask-the-expert" approach. Pediatric oncologists and radiotherapists from 21 European countries participated.

We found out that several positive initiatives, both national and international, are being taken to implement RTQA in the treatment of pediatric patients across Europe. However, there is still room for improvement, for which we proposed five key measures: Creating a European RTQA guideline for pediatric CNS tumors, improving the collaboration between pediatric oncologists and radiotherapists, building a European central storage system for RT data, implementing international RTQA platforms such as QUARTET, and promoting European referral networks to reduce inequality across countries. These measures may take years to be fully implemented, but they will hopefully contribute to improve the still dismal outcome of pediatric patients with CNS tumors.

Overall, this thesis shows that there are several aspects to be improved in the management of pediatric patients with CNS tumors. Our set of proposed measures constitutes a pragmatic attempt to tackle the issue, with a three-level approach: local, national and international. Moreover, most of these measures transcend tumor-type specificity and hence could be applied across different

CNS tumors, particularly across embryonal tumors. We hope this work will contribute to the global improvement of survival and quality of life of children and adolescents with CNS tumors.

VII. CONCLUSIONS

The conclusions from this thesis are listed below:

Research Project #1:

I) The global outcome of the real-world cohort of pediatric patients with medulloblastoma analyzed in this study is similar to the outcome observed in Spanish and European population-based studies.

II) Several measures to improve the multidisciplinary management of pediatric patients with medulloblastoma have been proposed, and include implementing a quality assurance system, maximizing the inclusion in international clinical trials, expanding the local Clinical Trials Unit, establishing a central pathology review, accelerating the translation of the new molecular knowledge into daily practice through the use of up-to-date biological markers, and implementing a neurocognitive and QOL evaluation program.

III) A set of 27 quality indicators to evaluate the management of pediatric patients with embryonal CNS tumors has been developed.

Research Project #2:

IV) Survival rates of the national, real-world cohort of pediatric patients with CNS-PNET have been lower than the rates in collaborative clinical trials.

V) This study has served to identify specific aspects to improve in the care of patients with CNS-PNET, namely establishing a common national strategy, implementing referral networks, and incorporating new molecular knowledge into routine clinical practice.

VI) A retrospective molecular analysis of archival tumor samples available for this patient cohort has been started in collaboration with European reference centers, in an international ongoing study for diagnostic re-evaluation of CNS-PNET with methylation profiling.

Research Project #3:

VII) Initiatives to implement RTQA, both at national and international levels, are being developed to improve outcomes of the treatment of pediatric patients with CNS tumors across Europe.

VIII) As a result of the analysis about the current practices of RTQA across Europe, five key measures were proposed: Creating a European RTQA guideline for pediatric CNS tumors, improving the collaboration between pediatric oncologists and radiation oncologists, building a European central storage system for RT data, implementing international RTQA platforms such as QUARTET, and promoting European referral networks to reduce inequality across countries.

CONCLUSIONES EN ESPAÑOL

Las conclusiones de esta tesis se enumeran a continuación:

Proyecto de Investigación #1:

I) La supervivencia global de la cohorte tipo "mundo real" de pacientes pediátricos con meduloblastoma analizada en este estudio es similar a la observada en estudios poblacionales españoles y europeos.

II) Se proponen diversas medidas para mejorar el manejo multidisciplinar de los pacientes pediátricos con meduloblastoma: implementar un sistema de control de calidad, maximizar la inclusión en ensayos clínicos internacionales, expandir la Unidad de Ensayos Clínicos local, establecer una revisión central de la anatomía patológica, acelerar el traspaso del nuevo conocimiento molecular a la práctica clínica a través del uso de biomarcadores, e implementar un programa de evaluación de la función neurocognitiva y de la calidad de vida.

III) Se ha desarrollado un set de 27 indicadores de calidad para evaluar el manejo de los pacientes pediátricos con tumores embrionarios del sistema nervioso central.

Proyecto de Investigación #2:

IV) Las tasas de supervivencia de la cohorte nacional tipo "mundo real" de pacientes pediátricos con tumores PNET del sistema nervioso central han resultado más bajas que las tasas observadas en ensayos clínicos colaborativos.

V) Este estudio ha servido para identificar aspectos específicos a mejorar en el cuidado de los pacientes con tumores PNET del

sistema nervioso central, concretamente: establecer una estrategia nacional común, implementar redes de colaboración y centros de referencia, e incorporar el nuevo conocimiento molecular a la práctica clínica rutinaria.

VI) Se ha iniciado un análisis molecular retrospectivo de las muestras tumorales de archivo disponibles para esta cohorte de pacientes, en colaboración con centros de referencia europeos, en un estudio internacional actualmente en marcha para la revaluación diagnóstica mediante perfil de metilación de los tumores PNET del sistema nervioso central.

Proyecto de Investigación #3:

VII) Se están desarrollando en Europa diversas iniciativas para implementar un sistema de control de calidad de la radioterapia tanto a nivel nacional como internacional, con el fin de mejorar los resultados del tratamiento de los pacientes pediátricos con tumores del sistema nervioso central.

VIII) Como resultado del análisis sobre las prácticas de control de calidad de la radioterapia en Europa, se proponen cinco medidas clave: crear una guía europea para tumores pediátricos del sistema nervioso central, mejorar la colaboración entre oncólogos pediátricos y radio-oncólogos, construir un sistema central europeo de almacenaje de datos sobre radioterapia, implementar plataformas internacionales de control de calidad de la radioterapia (tales como QUARTET), y promover redes de colaboración y derivación europeas para disminuir la desigualdad entre países.

VIII. APPENDICES

Appendix 1

Survey questionnaire: Current practices in radiotherapy for the treatment of pediatric patients with CNS tumors across Europe

1. In your country: How many (public) centers treat pediatric patients with cancer? (Response: Number)
2. In your country: How many (public) centers treat pediatric patients with brain tumors? (R: Number)
3. In your country: How many (public) centers treat pediatric brain tumor patients with radiotherapy (excluding particle therapy)? (R: Number)
4. What is your opinion regarding the following statement about radiotherapy in your country: "There is a known and well-established national referral network for the radiotherapy treatment of pediatric patients." (R: Likert Scale with these five options: Strongly disagree – Disagree – Neutral – Agree – Strongly agree)

   #4: Please, provide a short explanation (R: Text. Not mandatory)
5. Does your country have a national pediatric radio-oncologists society? (R: Yes/No)
6. How would you qualify the level of involvement of pediatric radio-oncologists in the meetings and activities of the national pediatric oncology society? (R: Likert Scale with these five options: Insufficient – Somewhat insufficient – Neither insufficient nor sufficient – Somewhat sufficient – Sufficient)

   #6: Please, provide a short explanation (R: Text. Not mandatory)
7. Do national consensus guidelines exist in your country for the treatment of pediatric brain tumors? (R: Yes/No)

a. If Yes: Do they include RTQA (radiotherapy quality assurance) recommendations? (R: Yes/No)

   #7a: Please, provide a short description of the guideline(s) (R: Text. Not mandatory)

8. Are you aware of any national (or local) radiotherapy quality assurance programs for the treatment of pediatric brain tumors? (R: Yes/No)
   a. If Yes: Please, indicate the name and provide a short description of the program(s) (R: Text)
9. In your country: Is there a central storage system, such as a national registry for radiotherapy data? (R: Yes/No)
   a. If Yes: Are the complete DICOM radiotherapy plans collected as part of the data? (R: Yes/No)
10. Do your patients have access to a particle therapy facility? (Nationwide or elsewhere, supported by the public health system) (R: Yes/No)

    #10: Please, provide a short explanation (R: Text. Not mandatory)
11. Would you say that all pediatric patients with brain tumors in your country are granted equal access to radiotherapy? (R: Likert Scale with these five options: Strongly disagree – Disagree – Neutral – Agree – Strongly agree)

    #11: Please, provide a short explanation (R: Text. Not mandatory)
12. Do you think that the patients would benefit from a European RTQA (radiotherapy quality assurance) guideline for pediatric brain tumors? (R: Likert Scale with these five options: Not at all – To a small degree – To a moderate degree – To a considerable degree – To a great degree)

    #12: Please, provide a short explanation (R: Text. Not mandatory)
13. Comments (R: Text)

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